IHR (2005) Compliance: Laboratory Capacities and Biological Risks

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The International Health Regulations (2005) – An Overview

In 2005, the United States and the other Member States of the World Health Organization (WHO) agreed to a new approach to global health security. Recognizing that international agreements rooted in the nineteenth century no longer sufficiently addressed the health threats posed by novel, emerging, and reemerging pathogens such as severe acute respiratory syndrome (SARS) and highly pathogenic H5N1 avian influenza, the World Health Assembly (WHA) adopted the revised International Health Regulations [IHR (2005)].[1] The revised IHR entered into force in June 2007. IHR (2005) obligate the now-196 States Parties to develop the core capacities required to detect, assess, report, and respond to public health emergencies of international concern. The regulations cover biological, chemical, radiological/nuclear, and other threats to public health, regardless of origin (naturally, accidentally, or deliberately released).

Over the past decade, governments, WHO, and international partners have devoted resources to the implementation of IHR (2005) as a framework for achieving global health security. The IHR (2005) agreement emphasizes the obligations of States Parties to develop, strengthen, and maintain the core capacities needed to detect and respond rapidly to emerging events from the national to the local level, as defined in Annex 1 of the agreement (Figure 1).

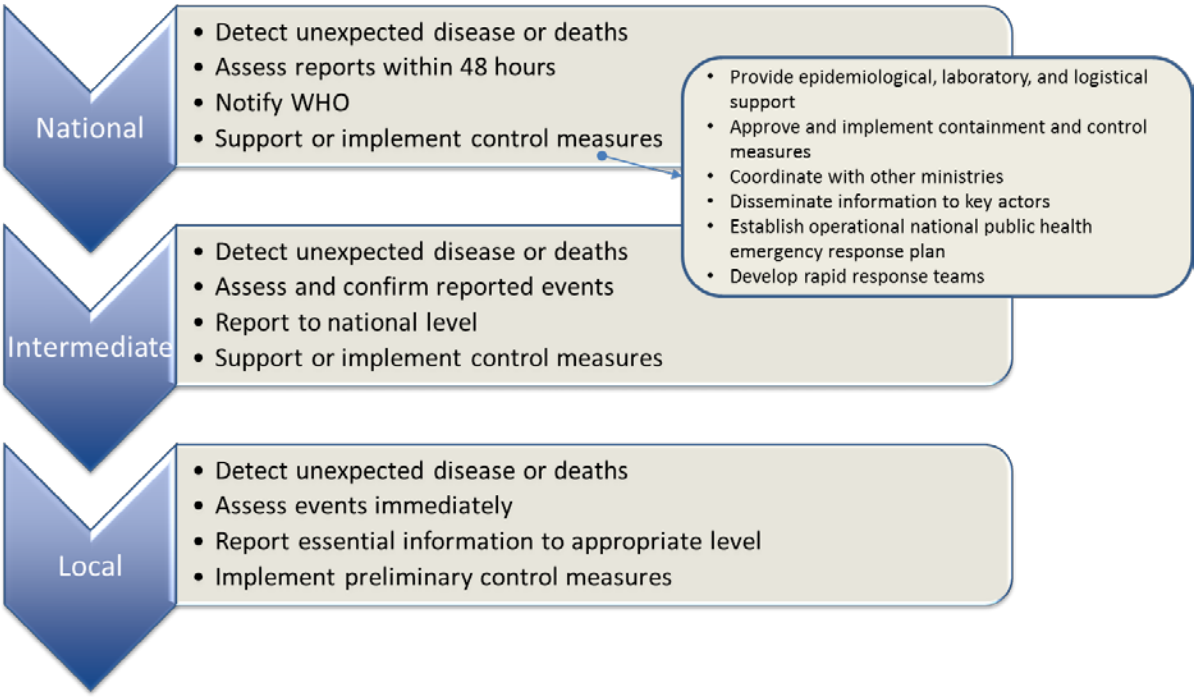

Figure 1: Functional capabilities that must be achieved by States Parties to comply with IHR (2005)
Source: summarized from IHR (2005) Annex 1

IHR (2005) also placed new responsibilities on WHO to facilitate information-sharing and coordinate international responses when needed, and on the global community to support worldwide implementation. IHR Article 44 calls on States Parties to collaborate in the development of global capacities to detect and respond to biological events by sharing logistical, technical, and financial

support through various mechanisms (bilateral, regional networks and WHO regional offices, and international organizations). Article 44 provides a mechanism for engaging international partners in cooperative capacity-building efforts that mutually reinforce the provisions of the Biological and Toxin Weapons Convention and UN Security Council Resolution 1540.

Box 1: IHR (2005) Core capacities and hazards

IHR Core Capacities:

1. National legislation, policy and financing
2. Coordination and NFP communications
3. Surveillance
4. Response
5. Preparedness
6. Risk communication
7. Human resources
8. Laboratory

Other obligations/Potential Hazards:

9. Points of entry
10. Zoonotic events
11. Food safety
12. Chemical events
13. Radiation emergencies

To help States Parties and their international partners translate the IHR core capacity requirements into measurable activities, WHO developed tools that include the WHO IHR Core Capacity Monitoring Framework and the corresponding WHO IHR Monitoring Tool (IHRMT), initially published in late 2010 and updated annually through 2013.[2] The Monitoring Framework identifies country-level indicators for eight core capacities, points of entry, and other hazards in addition to epidemic-prone and emerging infectious diseases (Box 1). The Monitoring Tool is intended to be used by national authorities to self-assess progress toward these country-level indicators for reporting to WHA, and to use in national planning. States Parties agreed to report their IHR implementation status to WHO by June 2012, either affirming that they had achieved the IHR core capacities or requesting a two-year extension to meet their obligations. Despite significant worldwide progress toward building core capacities, only 40 States Parties reported that they had fully implemented IHR (2005) by June 2012. By late 2013, 118 States Parties had successfully requested an extension through June 2014; the rest failed to support their requests with a national action plan (or submitted no report at all).[3] Many nations either reported full implementation or requested a second, and final, 2-year extension request by the June 2014 deadline, but as of August 2014, WHO had not yet announced how many States Parties would require additional time to implement the IHR core capacities effectively.

IHR (2005) and Biological Risk Management

The country level indicators detailed in the Monitoring Framework include attributes of a laboratory system capable of identifying and confirming priority events promptly, reliably, and safely. Clinical and public health laboratories in developing regions (particularly at the sub-national level) often lack the resources to test for priority diseases and events, delaying the detection of public health threats. Establishing access to appropriate screening, diagnostic, and confirmatory testing, either through domestic capacities or through agreements with outside laboratory systems, is critical to supporting effective disease surveillance and to achieving IHR compliance.

However, developing such capacities domestically may unintentionally create new risks to laboratory workers, the environment, and the broader global community. For example, establishing laboratory

capabilities to conduct tests that include propagation of pathogens increases the risk that laboratory workers could be unintentionally exposed to infectious agents, some of which have the potential for spread within the community, or that the pathogens could be vulnerable to unauthorized access, creating the potential for loss, diversion, or deliberate misuse.

Recognizing this paradox, WHA adopted a second resolution in 2005 that called for Member States and WHO to mobilize resources and technical guidance necessary to enhance laboratory biosafety worldwide. WHA Resolution 58.29 acknowledged that "the release of microbiological agents and toxins may have global ramifications…[and]…the containment of microbiological agents and toxins in laboratories is critical to preventing outbreaks of emerging and re-emerging diseases.[4]

As national governments and their international partners invest in laboratory capacity-building to strengthen capacities to detect, assess, report, and respond to biological events and other public health emergencies of international concern, these global biological security and health security risks must be considered in balance. Expanding the number of labs worldwide capable of performing sophisticated diagnostic testing and research increases the chances of a biological exposure or release occurring, with potential implications for the local, regional, or even the global community. On the other hand, establishing reliable and appropriate testing capabilities at each level of a national laboratory system reduces the risk that a natural, accidental, or deliberate outbreak might go undetected in the stages when prompt action could contain the event, or at least mitigate the consequences. Strategies aimed at enhancing laboratory capacities under IHR (2005) assume the necessity of taking on manageable, predictable risks in biosafety and biosecurity to allow health systems to identify, characterize, and respond to unpredictable, unmanageable risks more effectively.

The IHR Monitoring Framework emphasizes the need to develop risk-based biological safety and security capacities for public health laboratory systems. While this guidance provides necessary flexibility, countries also face challenges in developing a systematic risk-based approach to biosafety and biosecurity across a complex, tiered laboratory system. Many existing tools for biological risk assessment focus on risks at the level of a facility or laboratory. Although such granular risk assessments ultimately support adoption of appropriate measures at the local level, national laboratory capacity-building strategies that set minimum standards for diagnostic testing and commensurate biorisk mitigation measures at each level of a tiered, integrated laboratory system can help national decision makers and their international partners determine priorities for equipment, materials, and training.

WHO, the United States and other high-income governments, the European Union, and other international organizations have developed biosafety and biosecurity risk mitigation recommendations. However, much of the guidance embraced by high-income states and funding organizations derives from a paradigm developed for biomedical research and industrial laboratories, which face different risks and foster a different culture than diagnostic laboratories. Low- and middle-income countries frequently grapple with the challenges of developing national legislation and/or regulatory frameworks for biorisk management when the costs of implementation might not be sustainable – or the regulations themselves enforceable – in the local context. Historically, the priorities of external funders have often

driven assistance for laboratory biological risk management programs in developing regions, sometimes giving rise to extensive and expensive physical controls that cannot be maintained by national governments.

One avenue to understanding the general risks incurred when countries strengthen their diagnostic laboratory networks under IHR (2005) is to consider the capacities that must developed at each level of a tiered national laboratory network to identify priority diseases reliably and promptly. To this end, we have developed a model that estimates the degree of risk incurred by manipulation of priority pathogens for appropriate screening, diagnostic, or confirmatory tests for a notional laboratory system from sample collection to waste management. We also reviewed the guidance, tools, and risk mitigation strategies available in each region. With this information, we developed a typology that describes the general biorisk profile of laboratories at each level of a tiered national system that has been adequately prepared to detect priority communicable diseases, and identify general risk mitigation strategies.

BACKGROUND

What Are the IHR (2005) Laboratory Capacity Requirements?

Rather than prescribe specific activities that States Parties must implement to achieve compliance, the IHR (2005) agreement describes a general timeline and functional capabilities. Annex I of the IHR (2005) outlines the obligations on States Parties to strengthen their existing national systems to detect, report, notify, verify, and respond to potential public health emergencies of international concern at each level of government. The core capacity requirements at the national level include "laboratory analysis of samples (domestically or through collaborating centres)."[5]

The IHR Core Capacity Monitoring Framework (2013 revision) describes five country-level indicators for Laboratories (Core Capacity 8):

- A coordinating mechanisms for laboratory services is established;
- Laboratory services are available to test for priority health threats;
- Influenza surveillance is established;
- Laboratory biosafety and laboratory biosecurity (biorisk management) practices are in place and implemented; and
- Laboratory data management and reporting is established.[6]

States Parties determine whether or not they have met these country-level indicators by comparing their current functional capabilities to a series of attributes – programs, policies, or processes grouped under each country-level indicator in the IHR Monitoring Framework. These attributes are presented in the IHR Monitoring Tool for use by each National IHR Focal Point in conducting an annual self-assessment, primarily for reporting to WHO (results are aggregated annually for a progress report to WHA) but can be used additionally for national planning purposes. The attributes are categorized as foundational (-1), inputs and processes (1), outputs and outcomes (2), and additional achievements (3). States Parties have fully implemented the IHR, functionally reaching compliance, when they have achieved all of the attributes through level 2 for each core capacity.

Table 1: IHR Core Capacity Monitoring Framework – Laboratory Global Indicators and Attributes (Core Capacity 8) [7]	
Indicator	**Attributes**
A coordinating mechanism for laboratory services is established.	• A laboratory focal point identified for coordinating laboratory services • A national Plan of Action that includes essential functions of laboratories, minimum standards and licensing/registration, is available • Up to date policies disseminated to diagnostic laboratories, specifying minimal requirements in authorized laboratory services
Laboratory services available to test for priority health threats.	• A policy to ensure the quality of laboratory diagnostic capacities (e.g. licensing, accreditation, etc.) • National laboratory quality standards/guidelines are available • Access to networks of international laboratories to meet diagnostic and confirmatory laboratory requirements and support outbreak investigations for events specified in Annex 2 of IHR • National laboratory capacity to meet diagnostic and confirmatory laboratory requirements for priority diseases • Up to date and accessible inventory of public and private laboratories with relevant diagnostic capacity available • National reference laboratories participate successfully in External Quality Assessment schemes for major public health disciplines for diagnostic laboratories • More than 10 non-AFP (Acute Flaccid Paralysis) hazardous specimens per year referred to national reference laboratories for examination • National reference laboratories accredited to international standards or to national standards adapted from international standards • National regulations are compatible with international guidelines in force for the packaging and transport of clinical specimens • Functional system for collection, packaging and transport of clinical specimens • Sample collection and transportation kits been pre-positioned at appropriate levels for immediate mobilization during a PH event • Staff at national or relevant levels trained for the safe shipment of infectious substances according to international standards (ICAO/IATA) • Processes for shipment of infectious substances when investigating an urgent public health event consistently meet ICAO/IATA standards • Clinical specimens from investigation of urgent public health events are delivered to appropriate national or international reference laboratories within the appropriate timeframe of collection for testing or transport • At least 10 hazardous specimens per year is shipped internationally to a collaborating laboratory as part of an investigation or exercise
Influenza surveillance is established.	• Access to influenza testing, nationally or internationally • Rapid virological assessment of severe acute respiratory infections is in place • Participates in Global Influenza Surveillance Network, with regular submission of viral isolates for analysis

Laboratory biosafety and laboratory biosecurity (biorisk management) practices are in place and implemented.	• Biosafety guidelines accessible to laboratories • Regulations, policies or strategies for laboratory biosafety are available • A responsible entity is designated for laboratory biosafety and laboratory biosecurity • Relevant staff are trained in laboratory biosafety and laboratory biosecurity guidelines • An institution or person responsible for inspection (could include certification of biosafety equipment) of laboratories for compliance with biosafety requirements is identified • Biorisk assessment is conducted in laboratories to guide and update biosafety regulations, procedures and practice, including for decontamination and management of infectious waste
Laboratory data management and reporting is established.	• Priority pathogens for laboratory based surveillance are identified • Standard reporting procedures between laboratory services and the surveillance department, including timeliness requirements by class of pathogen, are established • SOPs for data management, data security and data quality exist at diagnostic laboratories • Analysis of laboratory data with reports disseminated to relevant stakeholders is done

By including a single attribute that sweepingly encompasses all "national laboratory capacity to meet diagnostic and confirmatory laboratory requirements for priority diseases," the IHR Core Capacity Monitoring Framework and IHRMT confirm that States Parties must develop or otherwise obtain access to the laboratory capacities required to diagnose and confirm priority health threats in a safe, reliable, and timely way, but leave the mechanisms up to national decision makers. Regional priority diseases for sub-Saharan Africa, Southeast Asia, and the Middle East/North Africa regions are described in Appendix 1 of this report.

What Are the IHR (2005) Priority Diseases?

Rather than a specific list of priority health threats, the IHR (2005) incorporate an algorithm to help States Parties assess whether or not an event constitutes a potential public health emergency of international concern (or PHEIC) that must be notified to WHO. The algorithm guides decision makers through a set of simple questions:

- Is the public health impact of the event serious?
- Is the event unusual or unexpected?
- Is there a significant risk of international spread?
- Is there a risk for international trade restrictions?

If the answer to two or more of these questions is yes, the IHR direct States Parties to notify WHO. This flexibility allows risk assessment of novel emerging diseases and consideration of context. An outbreak that might be considered unusual or a serious threat to public health in one area might be routinely encountered or easily managed in another, depending on local disease burden and resources. The decision-making algorithm, which is encompassed in Annex 2 of IHR (2005), also includes a list of four specific diseases that are "always notifiable" to WHO under IHR (2005), regardless of context.

Box 2: Diseases that must always be reported to WHO as public health emergencies of international concern (PHEIC) according to IHR Annex 2

Diseases that are unusual or unexpected and may have serious public health impact

1. Smallpox
2. Poliomyelitis due to wild-type poliovirus
3. Human Influenza caused by a new subtype
4. Severe acute respiratory syndrome (SARS)

The guidance in the IHR Annex 2 decision instrument identifies a second category of diseases or events of concern based on their potential for serious public health impact and ability to spread internationally. Annex 2 directs national authorities to assess any events involving these diseases using the decision algorithm, implying an extra level of scrutiny for this short list of diseases of historical and regional significance. In a 2010 protocol designed to help States Parties assess national surveillance and response capacities, WHO identified an almost identical list of diseases as priority diseases for which States Parties should establish diagnostic and confirmatory testing capabilities.[8]

Box 3: Diseases with potential for severe impact and rapid spread per IHR Annex 2

- Cholera
- Plague
- Yellow fever
- Viral hemorrhagic fevers (e.g., Ebola, Lassa, Marburg)
- West Nile fever
- Anthrax*
- Other diseases that are of special national or regional concern, such as dengue fever, Rift Valley fever, and meningococcal disease.

* Included in WHO Protocol for *Assessing National Surveillance and Response Capacities for the International Health Regulations (2005) in Accordance with Annex 1 of the IHR: A Guide for Assessment Teams* but not in IHR Annex 2.

Functions in a Tiered, Integrated Laboratory System

Neither the IHR (2005) agreement nor the IHR Monitoring Tool includes a checklist of specific laboratory tests or facilities that must be implemented. Instead, the regulations and the supporting technical guidance developed by WHO advise States Parties to achieve access to the diagnostic and confirmatory testing capabilities required to detect priority diseases. This could be attained entirely through formal agreements between governments and institutions to allow access to laboratory testing across borders (a feasible arrangement, for example, for island nations with small populations), or by developing domestic capacities to conduct appropriate screening, diagnostic, and confirmatory testing for priority diseases at each level of the national health system.

To characterize these capacities, we reviewed currently accepted laboratory standards for screening, diagnostic, and confirmatory testing for the infectious diseases identified as priority diseases or events in sub-Saharan Africa, Southeast Asia, or the Middle East and North Africa (see Appendix 1). Sources included WHO laboratory manuals and other supporting technical guidance published either by WHO Headquarters or the regional offices; laboratory manuals and technical guidance published by the U.S. Centers for Disease Control and Prevention (CDC); protocols published by laboratory credentialing organizations; and protocols published by professional/technical organizations such as the American Society for Microbiology or the American Society for Clinical Pathology.

This guidance served as the framework for a matrix of screening, diagnostic, and confirmatory tests likely to be conducted at each level of a tiered, integrated laboratory system for all pathogen/diseases categorized as high-risk in the IHR assessment tool and supporting protocol, plus the additional priority diseases described above for each region.

In the absence of specific guidance on testing levels in the pathogen-specific technical protocols, we applied the logical framework of the consensus recommendations for laboratory harmonization developed in conjunction with the Maputo Declaration on Strengthening of Laboratory Systems. The Maputo Declaration resulted from a meeting of major stakeholders convened by WHO in 2008 to develop a consensus on the laboratory capabilities needed to support appropriate diagnosis and care of tuberculosis, malaria, and HIV at the population level in order to achieve the disease reduction targets in the Millennium Development Goals.[9]

Major partners in development and technical assistance (including the US Agency for International Development and the US Centers for Disease Control and Prevention) who participated in the Maputo consensus process also developed detailed operational recommendations that urged decision makers to harmonize the tests, supplies, and equipment available at each laboratory service level as part of a national laboratory strategic plan. This would include adopting minimal nationwide standards for diagnostic tests and services offered at four health services levels:

- Level I-Primary: rapid diagnostic testing and simple microscopy at health post and health center laboratories;
- Level II- District: additional microscopic staining and serology services in small referral hospitals;
- Level III-Regional/Provincial: in addition to the above, microbiology culture, biochemical testing, and drug susceptibility testing, as well as limited molecular diagnostics (PCR);
- Level IV-National/Multi-country Reference Laboratory: complete menu of confirmatory tests, including qualitative and quantitative nucleic acid testing and antimicrobial resistance testing.[10]

Although these standards explicitly addressed diagnostic services only for tuberculosis, malaria, and HIV, they provide a conceptual framework that can be extrapolated to other priority endemic, epidemic-prone, and emerging infectious diseases in resource-constrained settings, especially where WHO has not published disease-specific guidance.

Comprehensive Biorisk Management

The introduction of infection control, laboratory biosafety, and laboratory biosecurity measures can significantly reduce the risks posed at all stages of specimen collection and diagnostic testing. Biological risk challenges and general mitigation measures are outlined in Figure 2. For healthcare providers and laboratory workers who evaluate patients and collect and process patient samples, infection control and biosafety procedures can mitigate the risk of exposure to or release of pathogens.

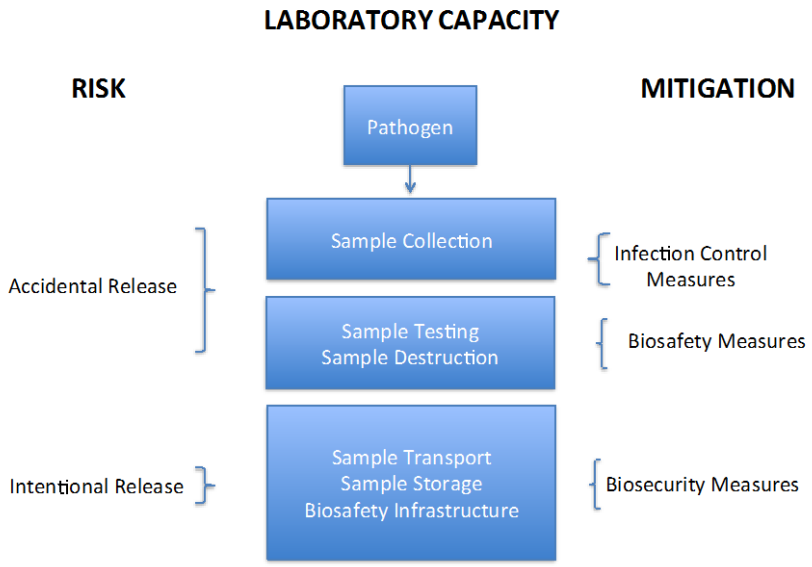

Figure 2: Biological risk mitigation relies on various measures at different stages of diagnostic testing.

Infection Prevention and Control in Healthcare Settings

In recent decades, several emerging infectious diseases – such as Ebola virus disease, SARS, and the Middle East Respiratory Syndrome-coronavirus (MERS-CoV) – have spread among patients, healthcare workers, and their contacts, undermining efforts to detect and respond rapidly to outbreaks. Core Capacity 4 (Response) in the WHO IHR Monitoring Framework addresses attributes related to infection prevention and control, or measures designed to limit the spread of infections in healthcare settings. Healthcare and laboratory workers who collect, process, and analyze patient specimens are at particular risk of exposure to communicable diseases. To minimize the risks of healthcare-associated infections in healthcare and laboratory workers, patients, and their contacts, including the emergence and spread of antimicrobial resistance, appropriate precautions must be taken during patient evaluation, transport, and treatment.

WHO has convened groups of experts to review and compile guidance for infection prevention and control measures.[11] This guidance includes transmission-based precautions for diseases such as specific acute respiratory infections that could constitute public health emergencies of international concern, to be undertaken in addition to the routine use of Standard Precautions for all patients.[12] The universal precautions (focused primarily on exposures to blood-borne pathogens) and standard precautions (which include all human tissue and fluids) developed by CDC illustrate national guidelines for intended to protect healthcare and laboratory workers, patients, and the community from the spread of healthcare-associated infections. Standard precautions include: 1) hand hygiene, 2) use of personal protected equipment, 3) safe injection practices, 4) safe handling of potentially contaminated equipment and surfaces, and 5) respiratory hygiene/cough etiquette. [13]

Laboratory Biosafety

While infection prevention and control measures primarily address human-to-human transmission of infectious diseases in clinical settings, laboratory biosafety measures pertain to efforts to reduce the risk of laboratory-acquired infections or other hazardous exposures during sample/specimen handling. WHO defines biosafety as the "the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release," [14] and laboratory biosafety and biosecurity attributes are included in the IHR Monitoring Framework. Laboratory biosafety measures include risk assessment, standard operating procedures, consistent use of safe techniques, training, personal protective equipment (PPE), engineering controls, and facility infrastructure and workflow. Primary containment measures include PPE and biosafety cabinets (workstations that rely on some combination of directional airflows, filters, and physical barriers to protect laboratory workers from exposure to pathogens during manipulations). Secondary containment includes barriers that prevent the spread of pathogens to other workers and to the community at large, such as airflow management and filtration and waste decontamination systems.[15]

The third edition of the WHO Laboratory Biosafety Manual, published in 2004, references CDC's standard precautions as the basis for safe handling of all specimens in the diagnostic laboratory.[16] The guidance outlines a risk-based approach to developing biosafety containment infrastructure and personnel practices to mitigate accidental exposure to a pathogen. To assist Member States in the development of functional laboratory capacity, WHO also developed the Laboratory Assessment Tool (LAT), most recently updated in 2012.[17] The LAT describes a framework for laboratory personnel to assess laboratory quality management, including facility and national biosafety practices, and includes measures to facilitate general biological risk assessments of individual facilities.

Additional precautions that address the specific risks of laboratory-acquired infections have been developed by several entities, including CDC and the U.S. National Institutes of Health (NIH), WHO, and the European Union. (See Appendix 2 for a list of published infection control and biosafety guidelines.)

The manual of Biosafety in Microbiological and Biomedical Laboratories (BMBL),[18]an advisory document developed by CDC and NIH, provides comprehensive recommendations for identification and reduction of risks in laboratories handling infectious pathogens. The recommendations in BMBL cover diagnostic and biomedical research laboratories. It outlines four containment levels, from biosafety level 1 to biosafety level 4 (BSL 1-4), outlining risk mitigation recommendations derived from a consequence-based methodology. These recommendations are referenced widely within the U.S. and internationally as a framework for minimizing the risk of laboratory-acquired infections.

Biosecurity approaches in diagnostic laboratories

While laboratory biosafety practices focus on mitigating the risks of accidental exposures and laboratory-acquired infections, laboratory biosecurity practices aim to prevent the loss, theft, misuse, diversion and/or intentional release of pathogens and toxins during handling or storage of biological materials. Biosecurity risk mitigation strategies include risk assessments, personnel surety processes, physical controls to prevent unauthorized access, pathogen storage management and inventory

systems, biohazard disposal, information security, safe and secure sample packaging and transport, and monitoring and accountability during specimen handling, analysis, and storage.

Generally, diagnostic laboratories face slightly different concerns than biomedical research facilities where high-consequence pathogens are studied. Patient specimens and environmental samples are highly impure, dilute, and relatively unstable sources of pathogens. The increasing sensitivity and specificity of many diagnostic technologies have diminished the amount of propagated specimens and purified controls required. Most diagnostic laboratories, particularly those below the central reference level, are not equipped for manipulation of large amounts of enriched pathogens.

Typical approaches to reduce biosecurity breaches have focused on improving physical security and access to dangerous pathogens. Measures to improve security at the facility level include proper sample packaging procedures, secure modes of sample transport, preventing access to work spaces and samples by unauthorized personnel, promoting awareness of biosecurity concerns through training for laboratory workers and managers, and instituting personnel reliability measures (as practical).

Biosecurity risks are generally considered to be minimal in most clinical laboratory settings due to the fact that patient samples are uncharacterized, impure, unstable, and contain relatively small amounts of pathogens. Research and industrial laboratories, and to some degree central reference laboratories that carry out culture and archiving of pathogen isolates, generally store larger quantities of more highly purified materials and therefore are a more likely target for theft or diversion. Nonetheless, because diagnostic laboratories may handle and store patient specimens or concentrated pathogen samples that could be misused, appropriate controls are necessary to prevent unauthorized access to pathogens and to reduce the possibility, however slight, that equipment and materials could be stolen or misused.

Comprehensive Biological Risk Management

In the last decade, the U.S., the United Kingdom, Japan, and a few other high-income countries have strengthened their own domestic laboratory biosecurity programs (such as the U.S. Select Agent Program), offering lessons learned for national biosecurity policy and regulatory frameworks. WHO's 2006 Laboratory Biorisk Management Guidance describes elements of a national biorisk program, but does not endorse specific standards.[19]

In 2012, WHO published a new five-year strategic framework outlining WHO's role in coordinating international efforts to develop standards for laboratory biological risk management.[20] These efforts primarily revolve around the setting of process standards for biological risk management organized by the European Committee for Standardization (CEN). In 2008, under the CEN Workshop process, a committee that included representatives of European and U.S. biosafety associations collaborated to generate a voluntary document, *CEN Workshop Agreement 15793 – Laboratory Biorisk Management,* (CWA 15793), which outlines international standards for laboratory biosafety and biosecurity that can be used as a basis for national biorisk management standards.[21] Committees also developed two supporting documents, CWA 16393:2012 (*Guidelines for the implementation of CWA 15793*)[22] and CWA 16335:2011 (*Biosafety Professional Competence*).[23] After minor updates in 2011, CWA 15793 is currently scheduled to expire at the end of 2014 per normal CEN processes, although the European Biosafety

Association and Sandia National Laboratories in the U.S. have collaborated to map a path forward for the guidance, from conversion to an ISO International Standard to more permanent stewardship of the document by another organization.[24] Sandia National Laboratories has also developed a laboratory biosafety risk assessment methodology tool (BIORAM) that takes into account specific laboratory requirements and pathogen-based risks.[25] This methodology has aided facilities in developing tailored biosafety approaches in diverse settings.

WHO has recognized that biological risk management is an integral part of functional laboratory capacity. The WHO IHR Monitoring Framework includes a number of country-level indicators to measure progress toward full achievement of the required Laboratory core capacities (Table 1). The country-level indicator for laboratory biosafety and biosecurity includes such attributes as development of a national laboratory biosafety regulatory framework, resources for certification of biosafety equipment, training in biosafety and biosecurity, and facility-level biorisk assessments.[26] Each of the States Parties to IHR has the responsibility to interpret these requirements within the national context, and to adapt existing guidance and systems accordingly.

Facility-based risk assessment will always provide information appropriate to developing and implementing a biorisk management plan tailored to an institution's specific infrastructure and workload. However, predictive information on the general nature of the biological risks faced by laboratory workers trained and equipped to perform a standardized testing menu could help stakeholders anticipate needs and integrate sustainable and appropriately scaled biological risk management strategies into strategic planning and budget development when strengthening diagnostic laboratory networks.

Estimating Biological Risks

Based on the IHR core capacity requirements and existing frameworks for biological risk management, we sought to address three primary questions:

- What is the general biological risk profile of diagnostic/public health laboratories at each health service level (1-4) within a national health system that has achieved IHR compliance (i.e., fully implemented the core capacity requirements)?
- Can any biological risks potentially created by strengthening and sustaining IHR-relevant diagnostic capacities in national laboratory systems be predicted reliably and generally enough to inform capacity-building strategies?
- What tools are needed and available to manage biological risks in public health laboratory networks, particularly in low and middle income countries?

To characterize the risks likely to be enhanced by strengthening of the capacities of a tiered, integrated national laboratory network to test for priority diseases, we sought to develop a matrix that would reflect pathogen-specific characteristics, risks posed by manipulation of samples at all stages of a laboratory system, and risks to the community and the individual. In this context, laboratory biological risk is defined as the risk to an individual and community posed by accidental or intentional release of a

pathogen during specimen collection, manipulation, analysis, and storage in a diagnostic laboratory system.

Priority Pathogens

Obviously, the pathogens being investigated in any laboratory play a key role in determining biological risks. Guidance such as the BMBL focuses on pathogen characterization to prescribe risk mitigation strategies and specific personal, engineering, and infrastructure protections. However, pathogens may pose different levels of risk depending on not only on transmission rates and routes, but on means of specimen collection and the diagnostic tests being conducted.

To develop a technical framework for assessing the biological risks for "IHR compliance," we first developed a notional priority disease list representing emerging, epidemic-prone, and high-priority endemic diseases frequently identified as public health threats in Sub-Saharan Africa, Southeast Asia, and the Middle East and North Africa. As detailed in Appendix 1, we reviewed reportable disease requirements developed by 9 ministries of health in low and middle income countries and by 1 sub-regional and 1 regional disease surveillance partnership to identify diseases/conditions frequently designated as notifiable within each region. The list includes the four always notifiable diseases under the IHR (2005) Annex 2 algorithm (smallpox, novel influenza strains, wild-type poliovirus, and SARS) as well as the "always consider" pathogens, which also appear on most priority disease lists from case study countries in the three regions. The notional "global" priority disease list extrapolated from all three regions is shown in Table 2.

Table 2: Global Priority Infectious Disease Threats – A Notional Reportable Disease List

Viral Diseases	Bacterial Diseases	Parasitic Diseases
• Chikungunya • Dengue • Viral Hemorrhagic Fevers (Ebola, Marburg, Rift Valley fever, Crimean-Congo Hemorrhagic fever, Lassa fever) • Hepatitis viruses (A, B, C, D, E) • HIV • Influenza • Japanese Encephalitis Virus‡ • Measles • MERS Co-V¶ • Polio • Rabies • SARS • Smallpox • Yellow Fever	• Anthrax • Brucellosis • Buruli ulcer* • Cholera • Diptheria‡ • Leprosy • Meningococcal meningitis • Plague • Shigella • Tuberculosis • Typhoid Fever	• Lymphatic filariasis* • Malaria • Onchoceriasis* • Trypanosomiasis*

*Sub-Saharan Africa only; ‡Southeast Asia only; ¶Middle East only

Functional laboratory capacities for notional priority disease list

Using the notional priority disease list, we reviewed current published guidance to identify the screening, diagnostic, and confirmatory tests recommended for each priority disease or pathogen, based on the best available current guidance. To identify "gold standard" laboratory testing algorithms, the research team reviewed laboratory manuals, standard operating protocols (SOPs), and other relevant technical guidance. The team considered guidance published by:

1. WHO Headquarters or WHO regional offices,
2. The U.S. Centers for Disease Control and Prevention (CDC),
3. Laboratory standards-based credentialing organizations (such as the Clinical and Laboratory Standards Institute), and
4. Professional organizations such as the American Society for Microbiology and the American Society for Clinical Pathology.

When multiple sources of guidance existed, the team selected the most authoritative source in the order listed above. These provided a information to define screening, diagnostic, and confirmatory tests likely to be conducted at each level of a tiered, integrated laboratory system for each priority disease. In the case of some diseases, WHO or other guidance describes the tests that should be conducted at the health facilities level, at intermediate (i.e., district or provincial) laboratories, and at the reference level. In the absence of pathogen-specific guidance, we applied the logical framework of the Maputo Declaration on Strengthening of Laboratory Systems (see page 11 of this report).

Table 3 illustrates this process for differential diagnostic testing in suspected cases of *Brucella*, a pathogen identified as a biosecurity concern for US biosecurity policies and one of the most notorious causes of serious laboratory-acquired infections.

Table 3. Determine diagnostic and specimen collection needs for each pathogen: *Brucella* spp.

Pathogen	Diagnostic Platforms	Specimen Collection	Service Level	Test Type
Brucella spp.	Rose Bengal test (P)	Serum (blood)	2	P
	Serum tube agglutination test	Serum (blood)	2	P
	ELISA (serology)	Serum (blood)	2	C
	Coombs indirect IgG	Serum (blood)	2	C
	Microagglutination test	Serum (blood)	2	C
	Immunocapture agglutination test (Brucella Capt)	Serum (blood)	2	C

	Blood culture, microbiological testing, and microscopy	Blood	3	C
	PCR	Blood	3	NS
	P = presumptive; C = confirmatory; NS = not yet standardized			

We repeated this process for each of the pathogens/diseases on the notional priority disease list and used this to develop an aggregated list of the tests for each pathogen, together with the most appropriate specimen collection techniques, needed to carry out appropriate screening, diagnostic, and confirmatory tests across a national diagnostic laboratory network.

Defining biorisk profiles

We applied standard epidemiological parameters used to measure the severity of disease to develop a qualitative scale for the risk of exposure/transmission to laboratory workers, and from laboratory workers to the community, incurred during collection and manipulation of specimens for each priority pathogen. These parameters included:

- Severity: average case fatality rate (CFR) – varies by pathogen;
- Transmissibility: basic reproductive rate (R0) – varies by pathogen; and
- Exposure risk based on specimen collection and manipulation – varies by diagnostic platform.

A detailed quantitative scoring scale is presented as a proof of concept in Appendix 4 that canonical risk equations based on these epidemiological and exposure parameters (based on studies of accidental exposures among healthcare workers, including laboratory workers) can be used to generate quantitative scores for planning and priority-setting by decision makers.

Qualitative, rapid assessment of biological risk data using previously published risk assessments, such as the BMBL, WHO, European, and American Biosafety Association (ABSA) risk scoring scales,[27] can be arrayed using the same logical framework to develop a biorisk profile at each level of a tiered, integrated diagnostic laboratory network associated with the development of a set of aggregated testing platforms, even in the absence of the specific estimates for transmission risk, etc., described in the detailed calculations in Appendix 4.

Table 4a-d estimate the biological risks posed at each health service level, assuming the development of appropriate screening, diagnostic, and confirmatory capacities for the notional priority disease list, using a binary coding scheme. In this scheme, platforms that potentially generate aerosols during pathogen manipulation received a score of +2 on a binary scale (0/2). Pathogens recognized as high-consequence due to transmissibility, virulence, case fatality rate, and availability of treatments (as indicated through designation at the Biosafety 3+/4 level within the BMBL framework) also received a score of +2, and those with the potential for human-to-human transmission received an additional +1 score.

The major laboratory exposure risk pathways were based on a broad review of the existing literature on laboratory exposures, which tend to be descriptive or qualitative rather than prospective, denominator-based studies. Where the literature described laboratory-acquired infections (LAI) based on known exposure risks/transmission pathways, we identified those as the major laboratory exposure risks, regardless of the number of cases reported globally, or of the exposure-based transmission risks. Based on these exposure risks, we identified needs for appropriate biorisk mitigation tools necessary for laboratory biosafety. We also developed an aggregate biorisk profile based on fully achieving capacities to conduct appropriate tests for the complete notional priority disease list at each level of a national laboratory system, including likely biosafety and biosecurity concerns at each laboratory level.

Table 4a: Risks at laboratory service level 1 by platform

The table below uses the following standard abbreviations:

P = parenteral; M = mucosal; I = ingestion; A = aerosol; PPE = personal protective equipment; BSC = biosafety cabinet; SP = standard precautions

Table 4a	**Service Level 1**							
Platform or procedure	**Disease**	**Specimen**	**Aerosol Transmission**	**BMBL Biosafety Level**	**ABSA Risk Group**	**Human-human transmssion**	**Major laboratory exposure pathway risk**	**Mitigation**
Rapid Diagnostic (& collection)	Cholera	Stool	no	2	2	0	M	SP
	Dengue	Serum	no	2	1 (Aus.) - 3 (Euro/UK)	0	P/M	SP
	Hepatitis	Serum	no	2	A: 2; B: 2/3; C: 3; D: 3; E: 2/3	0	P/M	SP
	HIV	Blood, serum, plasma, dried blood, urine, saliva	no	2	3	0	P	SP
	Lymphatic filariasis	Whole Blood	no	2	2	0	I	SP
	Malaria	Whole Blood	no	2	2	0	Minimal risk	SP
	Plague	Whole Blood	yes	2	3	0	M/I	SP
	Rabies	Brain (post-mortem)	yes	2	3	1	A	SP

Bacterial Staining (& collection)	Leprosy	skin smear	no	2	3	0	Minimal risk	SP
Light Microscopy (& collection)	Tuberculosis	Sputum	yes	2	3	0	A	SP; PPE
	Onchocerciasis	Skin snip/nodule biopsy	no	2	2	0	Minimal risk	SP
Specimen Collection only	Anthrax	Blood, skin lesion exudates, CSF, pleural fluid, sputum (occasionally urine & feces)	yes (rare)	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	M	SP; PPE
	Brucellosis	Blood, serum, bone marrow aspirate, tissue	yes	2	3	0	P	SP; PPE
	Buruli ulcer	biopsy, ulcer smear	no	2	2	0	Minimal risk	SP
	Chikungunya	Serum	no	3	2	0	Minimal risk	SP
	Crimean Congo hemorrhagic fever	Whole blood, serum, plasma, blood clot, or tissue	unlikely	4	4	1	P/M/A - HIGH	SP; PPE (enhanced IPC precautions)
	Diphtheria	Nose, throat, wound swab	yes			0	A	SP (plus vaccine)
	Dracunculiasis	No lab diagnostic	no	2	2	0	No specimen needed	
	Ebola virus disease	Whole blood, serum or plasma, skin or tissue from fetal cases	possibly	4	4	1	P/M/A - HIGH	SP; PPE (enhanced IPC precautions)
	Influenza	Nasopharyngeal swab, nasopharyngeal aspirate, tracheal swab, broncolavage fluid, blood	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	1	M/A	SP; PPE
	Lassa Fever	Whole blood, blood clot, tissues, serum or plasma	yes	4	4	1	P/M/A - HIGH	SP; PPE (enhanced IPC precautions)

	Malaria	Whole Blood from venipuncture or finger prick	no	2	2	0	Minimal risk	SP
	Marburg	Whole blood, blood clot, serum/plasma, or tissue	possibly	4	4	1	P/M/A - HIGH	SP; PPE (enhanced IPC precautions)
	Measles	Urine, nasopharyngeal aspirates, blood, throat swabs	yes	2	2	1	M/A	SP; PPE
	Meningococcal meingitis	CSF, blood	yes	2	2	0	P	SP
	Polio	Stool, pharynx swab	unknown	2	2	0	Minimal risk	SP
	Rift Valley fever	Whole blood, serum, plasma, blood clot, or tissue	yes	3	3	0	M/A	SP; PPE
	SARS	Stool specimen, plasma/serum, nasopharyngeal aspirates	yes	2 (3 for practices w/ high prob of aerosol)	3	1	A	SP; PPE (enhanced IPC precautions)
	Shigella	Stool sample	no	2	2	0	Minimal risk	SP
	Smallpox (rule out)	Biopsy specimen, scabs, vesicular fluid, pustule material, blood samples	yes	4	4	1	P/M	SP; PPE
	Trachoma	No lab diagnostic	no			0	No specimen needed	
	Trypanosomiasis	Whole blood, lymph node aspirates, cerebrospinal fluid	no	2	2	0	Minimal risk	SP
	Typhoid fever	Stool sample, blood, urine, bone marrow	no	2	2/3	0	P/I	SP
	West Nile fever	Whole blood, serum, plasma, tissue	no	2	3	0	P/A	SP; PPE
	Yellow Fever	Serum/Blood	no	3	3	0	P	SP; PPE

Table 4b: Risks at laboratory service level 2 by platform

The table below uses the following standard abbreviations:

P = parenteral; M = mucosal; I = ingestion; A = aerosol; PPE = personal protective equipment; BSC = biosafety cabinet; SP = standard precautions

Table 4b	**Service Level 2**							
Platform or procedure	**Disease**	**Specimen**	**Aerosol Transmission**	**BMBL Biosafety Level**	**ABSA Risk Group**	**Human-human transmssion**	**Major laboratory exposure pathway risk**	**Mitigation**
ELISA	Anthrax	Serum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	M/A	SP/PPE (centrifuge safety)
	Brucellosis	Serum	yes	2 for specimens; 3 for cultures		0	M/A/I	SP; PPE
	Buruli ulcer	Serum	no	2	3	0	Minimal risk	SP
	Chikungunya	Serum	no	3	3	0	Minimal risk	SP
	Dengue	Serum	no	2	1 (Aus.) - 3 (Euro/UK)	0	P	SP
	Hepatitis	Serum	no	2	A: 2; B: 2/3; C: 3; D: 3; E: 2/3	0	M/P	SP; PPE
	HIV	Serum	no	2	3	0	M/P	SP; PPE
	Lymphatic filariasis	Serum	no	2	2	0	I	SP
	Measles	Serum	yes	2	2	0*	P/A	SP; PPE
	Plague	Serum	yes	2	3	1	M/A/I	SP/PPE (centrifuge safety)

	SARS	Serum	yes	2 (3 for practices w/ high prob of aerosol)	3	1	A	SP; PPE (dilute specimens)
	Yellow Fever	Serum	no	3	3	0	M/P	SP; PPE
Bacterial Staining of heat fixed smear	Anthrax	Blood, pleural effusion, swab of lesion, cerebrospinal fluid	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	M	SP; PPE
	Brucellosis	Culture, bone marrow, CSF, wound/pus swab	yes			1	A/I	SP; PPE
	Meningococcal Meningitis	Cerebrospinal fluid	yes	2	2	1	M/A	SP - heat fixation/drying
	Plague	Bubo aspirate, sputum, blood smears, and tissues	yes	2	3	0	M	SP - heat fixation/drying
	Tuberculosis	Sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	A	SP - heat fixation/drying
	Buruli ulcer	Biopsy, smear from ulcer	no	2	3	0	Minimal risk	SP
Parasitic Staining	Lymphatic filariasis	Whole Blood	no	2	2	0	Minimal risk	SP
	Malaria	Whole Blood	no	2	2	0	Minimal risk	SP
	Trypanosomiasis	Whole blood, lymph node aspirates, cerebrospinal fluid	no	2	3	0	Minimal risk	SP
Serum Agglutination	Brucellosis	blood/serum	yes			1	A	SP/PPE
	Buruli ulcer	Blood, serum	no	2	3	0	Minimal risk	SP
Latex Agglutination	Meningococcal Meningitis	Cerebrospinal fluid (supernatant)	yes	2	2	1	A	SP/PPE (centrifuge safety)

Direct Immunofluorescence	Anthrax	Blood, pleural effusion, swab of lesion, cerebrospinal fluid	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	M/A	SP/PPE (centrifuge safety)
	Influenza	Throat swab, nasopharyngeal swab, nasal swab, nasopharyngeal aspirate, tracheal swab, broncolavage fluid, blood	yes	2 (seasonal); 3 (when HPAI-suspected)	2 (higher for HPAI strains)	1 (for NPA spec.)	M/A	SP/PPE
	Plague	Bubo aspirate, sputum, blood smears, and tissues	yes	2	3	1 (for aspirate)	A	SP/PPE (centrifuge safety)
Indirect Immunofluorescence	SARS	Serum	yes	2 (3 for practices w/ high prob of aerosol)	3	0	A	SP/PPE (centrifuge safety)
Haemagglutination Inhibition	Dengue	Serum	no	2	1 (Aus.) - 3 (Euro/UK)	0	P	SP/PPE
	Influenza	Blood/serum	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	0	M/A	SP/PPE
Rapid Diagnostic Test	Trypanosomiasis	Whole blood, lymph node aspirates, cerebrospinal fluid	no	2	2	0	Minimal risk	SP
LED Microscopy	Tuberculosis	Sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	A	SP - heat fixation/drying

Table 4c: Risks at laboratory service level 3 by platform

The table below uses the following standard abbreviations:

P = parenteral; M = mucosal; I = ingestion; A = aerosol; PPE = personal protective equipment; BSC = biosafety cabinet; SP = standard precautions

Table 4c	Service Level 3							
Platforms or procedures	**Disease**	**Specimen**	**Aerosol Transmission**	**BMBL Biosafety Level**	**ABSA Risk Group**	**Score**	**Risk**	**Mitigation**
Bacterial Culture	Anthrax	Swab of lesion, whole blood, fluids/aspirate, tissue, blot clot, serum, stool	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	M/A	SP/PPE/BSC
	Brucellosis	Blood (preferred), bone marrow, cerebrospinal fluid, wound swab, pus	yes			1	M/A/I	SP/PPE/BSC
	Buruli ulcer	Blood (preferred), bone marrow, cerebrospinal fluid, wound swab, pus, Biopsy, ulcer smear	no	2	3	0	Minimal risk	SP
	Cholera	Fecal specimen	no	2	2	0	I	SP/PPE
	Meningococcal Meningitis	Cerebrospinal fluid sediment or blood	yes	2	2	1	P/A	SP/PPE (centrifuge safety)
	Plague	Bubo aspirate, blood, cerebrospinal fluid, sputum	yes	2	3	1	M/A	SP/PPE/BSC
	Shigella dysenteriae	Fecal specimen	no	2	2	0	I	SP
	Tuberculosis	Deep chest sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP/PPE/BSC

	Typhoid fever	Fecal specimen, Blood, urine, bone marrow	no	2	2/3	0	P/I	SP
Bacterial Staining	Buruli ulcer	Subculture	no	2	3	0	Minimal risk	SP
	Meningococcal Meningitis	Subculture	yes	2	2	1	P/A	SP/PPE/BSC
	Typhoid fever	Subculture	no	2	2/3	0	P/I	SP
Biochemical Testing	Shigella dysenteriae 1	Subculture	no	2	2	0	I	SP
	Typhoid fever	Subculture	no	2	2/3	0	P/I	SP
PCR/Real-time PCR/Reverse Transcriptase PCR	Anthrax	Swab of lesion, whole blood, fluids/aspirate, tissue, blot clot, serum, stool	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	0	M	SP; PPE
	Brucellosis	Blood	yes			0	M/A/P	SP; PPE
	Buruli ulcer	Biopsy, ulcer smear	no	2	3	0	Minimal risk	SP
	Lymphatic filariasis	Whole blood	no	2	2	0	Minimal risk	SP
	Meningococcal Meningitis	Cerebrospinal fluid, blood	yes	2	2	0	M/A	SP; PPE
	Chikungunya virus	Serum	no	3	3	0	A	SP
	Dengue	Tissues, whole blood, serum, plasma	no	2	1 (Aus.) - 3 (Euro/UK)	0	P/A	SP; PPE
	Influenza	Nasopharyngeal swab, nasopharyngeal aspirate, tracheal swab, bronco lavage fluid, blood	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	0	M/A	SP; PPE
	Hepatitis	Blood	no	2	A: 2; B: 2/3; C: 3; D: 3; E: 2/3	0	P/A	SP; PPE

	HIV	Serum/plasma; blood	no	2	3	0	P	SP; PPE
	Measles	Urine, nasopharyngeal aspirates, blood, throat swabs	yes	2	2	0	M	SP; PPE
	Polio	Virus isolated from stool sample	unknown	2	2	0	I	SP
	Rabies	Saliva, cerebrospinal fluid, serum	yes	2	3	0	M	SP; PPE
	SARS	Stool, nasopharyngeal aspirates	yes	2 (3 for practices w/ high prob of aerosol)	3	0	M/A	SP; PPE
	Yellow Fever	Serum/Blood or tissue	no	3	3	0	P	SP; PPE
Serum Agglutination	Cholera	Subculture from fecal specimen	no	2	2	0	I	SP
	Meningococcal Meningitis	Fresh subculture from blood agar plate	yes	2	2	1	M/A	SP; PPE; BSC
	Shigella dysenteriae 1	Fresh subculture	no	2	2	0	I	SP
	Typhoid fever	Subculture on nonselective agar	no	2	2/3	0	P/I	SP
Neutralization Test	Polio	Viral isolate from stool sample	unknown	2	2	0	I	SP
	Influenza	Blood/serum	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	1	M/A	SP; PPE; BSC
Oxidase Test	Meningococcal Meningitis	Fresh subculture from blood agar plate	yes	2	2	1	M/A	SP; PPE; BSC

Catalase Test	Tuberculosis	Slant Culture	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC
Carbohydrate Utilization	Meningococcal Meningitis	Subculture	yes	2	2	1	M/A	SP; PPE; BSC
Antimicrobial Susceptibility	Tuberculosis	Deep chest sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC
Line Probe Assay	Tuberculosis	Deep chest sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC
Niacin Test	Tuberculosis	Deep chest sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC
Nitrate Reduction Test	Tuberculosis	4 week old culture	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC
Gene XPERT	Tuberculosis	Deep chest sputum	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	A	SP; PPE; BSC

Table 4d: Risks at laboratory service level 4 by platform

The table below uses the following standard abbreviations:

P = parenteral; M = mucosal; I = ingestion; A = aerosol; PPE = personal protective equipment; BSC = biosafety cabinet; SP = standard precautions

Table 4d	Service Level 4							
Level IV	**Disease**	**Specimen**	**Aerosol Transmission**	**BMBL Biosafety Level**	**ABSA Risk Group**	**Score**	**Risk**	**Mitigation**
Immunohistochemistry	Anthrax	Pleural effusion, bronchial biopsy, lesion biopsy	yes	2 for non-aerosol; 3 for aerosol and lg quantities	3	1	M/A	SP; PPE; BSC
	Buruli ulcer	Biopsy	no	2	3	0	Minimal risk	SP
	Crimean Congo	Tissue or skin biopsy from fatal cases	unlikely	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Dengue	Tissue	no	2	1 (Aus.) - 3 (Euro/UK)	0	P	SP; PPE
	Ebola	Skin or tissue specimens from fatal cases	possibly	4	4	1	P/M/A - HIGH	SP; PPE; BSC
	Lassa Fever	Tissue or skin biopsy from fatal cases	yes	4	4	1	P/M/A - HIGH	SP; PPE; BSC
	Marburg	Tissue biopsy	possibly	4	4	1	P/M/A - HIGH	SP; PPE; BSC
	Rift Valley Fever	Tissue biopsy	yes	3	3	1	P/M/A	SP; PPE; BSC
	West Nile Fever	Tissue biopsy	no	2 (3 for bird dissection)	3	0	Minimal exposure to potential transmission routes w/ universal precautions	
	Yellow Fever	Post-mortem tissue	no	3	3	0	P	SP; PPE
ELISA	Crimean Congo	Whole blood, serum, plasma	unlikely	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Ebola	Whole blood, serum, or plasma	possibly	4	4	1	M/A	SP; PPE; BSC; centrifuge safety

	Lassa Fever	Whole, blood, serum and plasma	yes	4	4	1	P/M/A - HIGH	SP; PPE; BSC
	Marburg	Whole blood, blood clot, serum, or plasma	possibly	4	4	1	P/M/A - HIGH	SP; PPE; BSC
	Rift Valley Fever	Whole blood, serum, plasma, blood clot, or tissue	yes	3	3	1	P/M/A - HIGH	SP; PPE; BSC
	West Nile Fever	Whole blood, serum, plasma	no	2 (3 for bird dissection)	3	0	M/A	SP; PPE
Immunofluorescence	Rabies	Skin biopsy containing cutaneous nerves	yes	2	3	1	M/A	SP; PPE; centrifuge safety
RT-PCR	Crimean Congo	Whole blood, blood clot, serum/plasma, or tissues	unlikely	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Ebola	Whole blood, blood clot, serum/plasma, or tissue	possibly	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Lassa Fever	Whole blood, blood clot, tissues, serum or plasma	yes	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Marburg	Whole blood, blood clot, serum/plasma, or tissue	possibly	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	Rift Valley Fever	Tissue biopsy, whole blood, or blood clot	yes	3	3	1	M/A	SP; PPE; BSC; centrifuge safety
	Small Pox - RULE OUT	Biopsy specimen, scabs, vesicular fluid, pustule material, blood samples	yes	4	4	1	M/A	SP; PPE; BSC; centrifuge safety
	West Nile Fever	Whole blood, serum, tissue biopsy	no	2 (3 for bird dissection)	3	0	M/A	SP; PPE

Haemagglutination Inhibition	Influenza	Viral isolates	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	1	M/A	SP; PPE; BSC
Phage Lysis	Plague	Subculture	yes	2	3	0	M/A	SP; PPE; BSC
Viral Isolation	Chikungunya virus	Serum	no	3	3	0	M/A	SP; PPE; BSC; centrifuge safety
	Dengue	Serum, plasma, peripheral blood mononuclear cells, autopsy tissues	no	2	1 (Aus.) - 3 (Euro/UK)	0	M/A	SP; PPE; BSC; centrifuge safety
	Influenza	Nasopharyngeal swab, nasopharyngeal aspirate, tracheal swab, broncolavage fluid, blood	yes	2 (seasonal); 3 (HPAI or 1918-related work)	2 (though may be higher for some strains)	1	M/A	SP; PPE; BSC; centrifuge safety
	Polio	Stool, pharynx swab	unknown	2	2	1	I	SP; PPE; BSC
	Rabies	Skin biopsy, serum, cerebrospinal fluid, saliva	yes	2	3	0	A/I	SP; PPE; BSC
	SARS	Stool specimen, plasma/serum, nasopharyngeal aspirates	yes	2 (3 for practices w/ high prob of aerosol)	3	1	M/A	SP; PPE; BSC; centrifuge safety
	Yellow Fever	Serum/Blood	no	3	3	0	P	SP; PPE; BSC

For each of these detailed assay-based risk profiles based on the notional disease list, it is possible to generate an aggregated overview of biological risks (see Table 5).

Table 5. Score risks posed by aggregated pathogen tests at each service level

Service Level	Diagnostic Test	Risk Scores		Major exposure risk	Mitigation Tools
		Infectious	Communicable		
1	Rapid Test	+	+++	P/M	SP
1/2	Microscopy	++	+++	P/M	PPE
2/3	Agglutination	+	++	P/M	PPE
2/3	ELISA	++	++++	P/M	PPE
2/3	Bacterial culture and biochemical testing	++++	++++	P/M/A/I	PPE; BSC
2/3	PCR/RT-PCR	++	+++	P/M	PPE

P = parenteral; M = mucosal; A = aerosol; I = ingestion; PPE = personal protective equipment; BSC = biosafety cabinet; SP = standard precautions

General Biorisk Profiles

Based on these aggregated risk profiles, interviews with key stakeholders in the three priority regions, and existing biosafety and biosecurity guidance, we developed a set of general biorisk profiles for diagnostic laboratories at each level of a tiered, integrated laboratory system that can be used to help non-technical decision makers understand the general challenges at each level.

General Biorisk Profile - Health Service Level I Laboratory

General Overview

Health Service Level 1 (HSL 1) laboratories are part of the primary health care facilities that handle in- and out-patient screening for a community. Most often the laboratory is a single room used to collect patient samples (blood, swabs, sputum, urine, feces) with very limited laboratory equipment and little to no engineering controls. HSL 1 laboratories are limited in their diagnostic capabilities referring the majority of patient samples to levels 2-4 for diagnostic testing.

Diagnostic Capabilities

HSL 1 laboratories have very restricted diagnostic capabilities and are limited to sample collection, rapid diagnostic tests, and basic microscopy. Sample collection requires direct contact with patients who may expose laboratory staff to infectious pathogens. Sample collection methods require contact with blood, swabs (nose, throat, nasopharynx, tracheal, wound), urine, feces and possibly skin biopsies. Risk mitigation includes proper sample collection as well as capacities for sample referral and shipment as a majority of the diagnostic tests will be performed in level 2 and above.

Staff

Generally HSL 1 staff consists of laboratory technicians with little to no experience or technical training. There is a high level of turnover not only because properly trained staff seek higher paying positions but staffing is decided at higher levels across the ministry with little to no input from laboratory managers/ directors. Mitigation efforts can include employment and job placement policies as well as regular and mandatory training for staff on proper sample collection (process and transmission-based precautions), diagnostics, and sample referral/transport. SOPs should be developed and accessible to all staff.

Biosafety Risks

Major biosafety risks involve accidental exposure and/or intentional release during sample collection, handling, diagnostics, storage, and/or destruction. Risk mitigation can be performed through regularly scheduled training, providing SOPs for all laboratory activities (sample collection, laboratory techniques/diagnostics, sample disinfection/waste management) that are easily accessible to all laboratory staff and providing appropriate personal protective equipment (PPE) including gowns, face masks, gloves, and eye goggles. In addition staff should be offered all available vaccines against priority diseases.

Biosecurity Risks

The relative risk is minor. There is a small amount of unstable pathogen in patient samples collected at HSL 1. There is no risk of pathogen manipulation due to lack of equipment and technical expertise. Risk mitigation can be performed by restricted access to laboratory section of health facility.

General Biorisk Profile - Health Service Level 2 Laboratory

General Overview

Health Service Level 2 (HSL 2) laboratories are part of the district level referral hospitals. The hospitals are small intermediate referral facilities that serve inpatients. The laboratories have dedicated laboratory space and trained personnel. HSL2 labs provide test menus for diagnoses with multiple diagnostic platforms as well as coordinate HSL1 laboratory services.

Diagnostic Capabilities

HSL2 labs perform multiple diagnostic platforms including microscopy, microbiology culture, serology, and biochemical testing. Consolidating testing at HSL2 leads to the use automated equipment platforms as well as coordinate the services of HSL1 laboratories. Risk mitigation includes proper transmission-based precautions in handling of samples during isolation, culture and/or isolation.

Staff

Generally HSL2 staff consists of laboratory specialists and technicians with varying experience and technical training. Staff turnover remains an issue with trained staff seeking higher paying positions as well as staffing decisions made at higher levels across the ministry with little to no input from laboratory managers/ directors. Mitigation efforts can include employment and job placement policies as well as regular and mandatory training for staff on proper sample collection (process and transmission-based precautions), diagnostics, and sample referral/transport. SOPs should be developed and accessible to all staff.

Biosafety Risks

Major biosafety risks involve accidental exposure and/or intentional release during sample handling, diagnostics, storage, and/or destruction. Risk mitigation can be performed through regularly scheduled training, providing SOPs for all activities (laboratory techniques/diagnostics, sample disinfection/waste management) that are easily accessible to all laboratory staff and providing appropriate personal protective equipment (PPE) including: gowns, face masks, gloves, and eye goggles. In addition staff should be offered all available vaccines against priority diseases and proper engineering controls should be provided for isolation and culture.

Biosecurity Risks

The relative risk is moderate and lies in pathogen manipulation, culture techniques, and the vulnerability of the isolates and cultures. Risk mitigation can be performed by providing physical security to the laboratory space to prevent unauthorized access

General Biorisk Profile - Health Service Level 3 Laboratory

General Overview

Health Service Level 3 (HSL 3) laboratories are regional or provincial laboratories. The laboratories have dedicated space for specimen receipt, laboratory diagnostic testing, engineering controls for limited molecular testing, and trained personnel. HSL3 labs provide extensive test menus for diagnoses with multiple diagnostic platforms as well as coordinate HSL2 laboratory services.

Diagnostic Capabilities

HSL3 labs perform multiple diagnostic platforms including microscopy, microbiology culture, serology, biochemical testing, and limited molecular techniques, including PCR. Risk mitigation includes proper transmission-based precautions in handling of samples during isolation, culture and/or isolation.

Staff

Generally HSL3 staff consists of laboratory technician and specialists with some laboratory experience and technical training. As with HSL2 staff turnover is an issue with time-limited positions and staffing decisions made at higher levels across the ministry with little to no input from laboratory directors. Mitigation efforts can include employment and job placement policies as well as regular and mandatory training for staff on sample receipt, molecular diagnostics, engineering controls, and hazardous waste management. SOPs should be developed and accessible to all staff.

Biosafety Risks

Similar to HSL2, major biosafety risks involve accidental exposure and/or intentional release during sample handling, microbiology culture, molecular diagnostics, storage, and/or destruction. Risk mitigation can be performed through regularly scheduled training, providing SOPs for all activities (laboratory techniques/diagnostics, sample disinfection/waste management) that are easily accessible to all laboratory staff and providing appropriate personal protective equipment (PPE) including: gowns, face masks, gloves, and eye goggles. In addition staff should be offered all available vaccines against priority diseases and proper engineering controls should be provided for isolation and culture.

Biosecurity Risks

The relative risk is moderate and lies in the vulnerability of the isolates and cultures particularly with pathogen manipulation and culture. Risk mitigation can be performed by providing physical security to the laboratory space to prevent unauthorized access.

General Biorisk Profile - Health Service Level 4 Laboratory

General Overview

Health Service Level 4 (HSL 4) laboratories are national or multi-country reference laboratories. These laboratories are WHO testing laboratories that handle and store controlled pathogens. The laboratories have dedicated space for specimen receipt, laboratory diagnostic testing, engineering controls for molecular testing, and trained personnel. HSL4 labs provide a complete menu of confirmatory tests including qualitative and quantitative nucleic acid testing and antimicrobial resistance. HSL4 labs coordinate laboratory services for the entire country or for multiple countries.

Diagnostic Capabilities

HSL4 labs perform a complete menu of diagnostic platforms including microbiology culture, serology, biochemical testing, molecular techniques, and antimicrobial resistance testing. Risk mitigation includes proper transmission-based precautions in handling of samples during isolation, diagnostics, and destruction as well as proper training and PPE to prevent exposure to aerosols/droplets from culture manipulation.

Staff

HSL4 laboratories have senior laboratory specialists, laboratory specialists and assistants on staff. Training is crucial to retaining qualified staff. It is important to maintain scheduled, regular training for molecular diagnostics, standard precautions and transmission-based risks, biorisk assessment and mitigation, engineering controls including biosafety cabinets, laboratory equipment maintenance, and biohazardous waste management. SOPs and training should be regularly scheduled and accessible to all staff.

Biosafety Risks

Similar to HSL2 and HSL3, major biosafety risks involve accidental exposure and/or intentional release during sample handling, culture, molecular diagnostics, storage, and/or destruction. Risk mitigation can be performed through regularly scheduled training, providing SOPs for all activities (laboratory techniques/diagnostics, sample disinfection/waste management) that are easily accessible to all laboratory staff and providing appropriate PPE including: gowns, face masks, gloves, and eye goggles. In addition staff should be offered all available vaccines against priority diseases and proper engineering controls should be provided for isolation and culture.

Biosecurity Risks

The relative risk is moderate to high and lies in the vulnerability of the isolates and cultures to theft or diversion. Risk mitigation can be performed by providing physical security to the laboratory space including access controls, personnel surety, and an archiving strategy for specimens and isolates. The risk of pathogen theft and/or diversion is assessed higher than the threat of deliberate misuse.

Conclusions

Under IHR (2005), States Parties are required to develop core capabilities to detect and respond to potential public health emergencies of international concern. To model risk management under this framework, we employed a classical risk management equation:

Risk – Controls = Residual risk (Eq. 1)

In this context, the overall intent of laboratory biorisk management (LBR) under IHR (2005) is to develop functional capacities that reduce health security risks to a level (residual risk) that is acceptable to health workers at the facility level and to the international community. In this model, risk refers to existing risks to global health security (GHSR); controls refer to the attributes under Laboratory in the IHR (2005) Core Capacities Monitoring Framework (IHR CC); and residual risk (RR) refers to the risks remaining after full implementation of the laboratory biosafety/biosecurity attributes described in the IHR Monitoring Framework (implemented through practices or standards described in documents such as CWA 15793:2011 or the US BMBL). The equation that best describes the relationship between global health security risks and the standards encapsulated in the IHR CC Monitoring Framework is:

GHSR – IHR CC + LBR = RR (Eq. 2)

Ideally, the IHR CC will fully offset the initial GHSR. If we rearrange equation 2 and assume that IHR CC = GHSR, we obtain:

~~GHSR~~ + LBR = RR + ~~IHR CC~~ (Eq. 3)

Although it is unlikely that the initial global health security will reach 0, *Eq. 3* demonstrates the contribution of unmitigated laboratory biological risk to residual risk and underscores the importance of appropriate biological risk mitigation when developing laboratory capacity.

As national clinical laboratory systems are strengthened worldwide to improve abilities to detect, assess, report, and respond rapidly to biological events in accordance with the core capacity requirements under IHR (2005), policy-makers and public health officials must plan to manage novel biological risks that may be created by expanding diagnostic capacities for priority diseases. Clinical and public health laboratories function differently than research and industrial facilities, creating different working environments, pressures, and cultural norms.

While research laboratory workers generally work with pre-identified biological agents, and thus may avail themselves of existing guidance on handling hazardous materials (assuming awareness of and access to such resources), diagnostic laboratory workers frequently handle patient specimens containing unknown pathogens. Although the quantities of these pathogens may be small and impure, the inherent biological risk posed by any individual sample may not be known until after extensive testing has identified the disease-causing organism. Research laboratories tend to be built on traditional hierarchies, with a primary investigator guiding the laboratory intellectually (but not necessarily at the bench) while more senior trainees and professional technicians directly supervise early career trainees,

all motivated by professional development incentives that include publications and acquisition of continuing funding. In contrast, clinical and public health laboratories tend to be staffed by salaried laboratory technicians and technologists, driven by the need to support rapid clinical decision-making reliably and cost effectively (often through fee-for-service financing). Laboratory and public health stakeholders interviewed directly by the research team in priority regions (including Southeast Asia, the Middle East and North Africa, and sub-Saharan Africa) report high staff turnover, especially among health facilities in rural or underserved geographic areas, as laboratory professionals advance their careers or seek better amenities by moving among government public health/clinical laboratories or from the public to the private sector.

In low- and middle-income countries, laboratory worker protections (including vaccinations, access to health services and prophylactic countermeasures, adequate PPE, functional biosafety cabinets, and – above all – training) may be uneven at best. However, the gold standard of testing for most diseases and conditions identified as high priority at the national, regional, and global levels depends upon timely and reliable laboratory testing. Despite aspirations of skipping the "wet lab" for testing based purely on rapid diagnostic testing or molecular diagnostics using minute samples, national health systems still need adequate laboratory services, particularly at the first formal levels of health services where patients with priority diseases are likely to present, and robust systems for transporting specimens to reference laboratories for confirmatory testing.

Following standards- and transmission-based precautions is key for reducing the risks of laboratory acquired infections. Internationally accepted biorisk management frameworks (such as the US BMBL, WHO, and European biosafety scoring systems) provide quick frames of reference to the general risks posed by pathogens. However, much of the guidance developed to help implement these systems derives from systems designed for research and industrial laboratories that conduct high-risk operations with known pathogens, with support at the facility level. Additionally, many laboratory risk assessment tools measure risk at the level of the individual, not the community.

External partners in capacity-building projects often apply the standards used domestically in their own countries (for example, the BMBL standards for biosafety levels 1 -4) when supporting capacity-building to enhance laboratory biosafety and biosecurity with partner nations, including for diagnostic laboratories. The practice-based physical infrastructure and engineering controls adopted under these standards are often expensive to maintain, and ultimately not sustainable in low-resource countries. Substandard and under-maintained biosafety equipment poses a significant danger to workers and the community at large.

Our approach demonstrates the proof of concept that laboratory biosafety and biosecurity risks can be predicted, and planning and budgeting to mitigate such risks sustainably can be included in capacity-building strategies. For each pathogen designated as a priority disease at the national, regional, or global level, practical steps can be used to:

- Identify "gold standard" diagnostic algorithms for each priority pathogen;

- Determine most appropriate tests at each health systems level (e.g., district, provincial, national);
- Characterize the risks created by each pathogen in the context of specific diagnostic platforms;
- Identify biological risks and strategies for mitigation;
- Develop a general biorisk profile that can be used in planning for laboratory capacity building; and
- Develop a costing strategy for biological risk management that can be used across national laboratory systems.

Planning and budgeting for laboratory biological risk mitigation strategies can be strengthened using this systematic approach, and by applying nuanced approaches that consider costs and benefits in the context of the risks most likely to be encountered by appropriately equipped diagnostic laboratories that support rapid disease detection from the local to the national level.

Appendix 1: Regional Priority Diseases

National and regional priority diseases: sub-Saharan Africa

In 1998, the Member States of the WHO Regional Committee for Africa adopted a regional Integrated Disease Surveillance and Response (IDSR) strategy under resolution AFR/RC48/R2 to strengthen surveillance for and response to the diseases that cause disability and death throughout the African region. In 2006, the WHO Regional Office for Africa declared "application of the IHRs (2005) in the African Region will proceed in the context of the Integrated Disease Surveillance and Response (IDSR) strategy that the WHO Regional Committee for Africa adopted in 1998."[28] The majority of countries in the region (43 of 46) adopted the IDSR strategy, and WHO/AFRO worked with partner organizations such as the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID) to support implementation at every level of their health systems. In 2010, WHO/AFRO and CDC worked together to update IDSR technical guidance, expanding the scope of the tools to reflect IHR reporting requirements. The 2010 technical guidance includes a list of IHR/IDSR-relevant diseases, conditions, and events that countries are expected to adapt for their own use, according to national priorities and disease burden.[29] Table 2 lists the infectious diseases included in this guidance by category. (Although the technical guidance also included non-communicable diseases among these priority notifiable diseases for the first time, these do not appear immediately relevant to IHR reporting requirements. Also excluded are syndromes based on case definitions without laboratory confirmation, such as diarrhea in children under 5 years of age with dehydration.)

Priority diseases, conditions, and events for Integrated Disease Surveillance and Response in the WHO African Region – 2010			
Epidemic prone diseases	**Diseases targeted for eradication or elimination**	**Other major diseases, events or conditions of public health importance**	**Diseases or events of international concern**
Acute hemorrhagic fever syndrome (Ebola, Marburg, Rift Valley, Lassa, Crimean Congo, West Nile Fever)* Anthrax* Chikungunya Cholera* Dengue* Diarrhea with blood (*Shigella*) Measles Meningococcal meningitis Plague* Severe Acute Respiratory Infection Typhoid fever Yellow fever*	Buruli ulcer Dracunculiasis Leprosy Lymphatic filariasis Neonatal tetanus Onchocerciasis Poliomyelitis*	Acute viral hepatitis HIV/AIDS (new cases) Malaria Rabies Sexually transmitted illnesses Trachoma Trypanosomiasis Tuberculosis	**Human influenza due to a new subtype*** **SARS*** **Smallpox*** **Any public health event of international or national concern (infectious, zoonotic, food borne, chemical, radio nuclear, or due to unknown condition)***
Always notifiable or high-risk diseases under IHR (2005)			

Because this regional strategy has been adopted by the majority of sub-Saharan African countries, the IDSR priority disease list serves as a regional representation of the priority diseases, conditions, and events for which national laboratory systems must develop diagnostic and confirmatory testing capabilities under IHR (2005) in the WHO/AFRO region. Although some of the major diseases identified as regional priorities would not necessarily be reportable as PHEICs, they generally share diagnostic testing platforms with high-risk, epidemic-prone diseases that occur less frequently, and thus can be considered proxy diseases for laboratory testing and reporting capabilities.

National and regional priority diseases: Southeast Asia

The Member States of the WHO regional offices representing South and Southeast Asia and the Western Pacific (SEARO and WPRO, respectively) agreed in 2005 to adopt a shared strategic framework for building regional capacities for public health security. The Asia Pacific Strategy for Emerging Diseases (APSED), updated in 2010 to reflect IHR requirements as well as national capacity-building experiences, outlines strategic actions for national decision makers to consider in building IHR (2005) core capacities to detect, report, and respond to public health events.[30]

The Asia Pacific Strategy for Strengthening of Health Laboratory Services (2010–2015) provides a framework for laboratory assessments and capacity-building, but did not specifically list priority diseases for the region.[31] Table 3 lists national priority diseases for six nations representing the spectrum of economic development levels in Southeast Asia, along with the list of reportable diseases selected for reciprocal reporting by the six participating states of the sub-regional Mekong Basin Disease Surveillance cross-border network (Cambodia, Yunan and Guangxi provinces in China, Lao PDR, Myanmar, Thailand, and Vietnam). Diseases designated as reportable among 5 or more of the 7 lists are highlighted in blue.[1] Based on the frequency with which these diseases appear on nationally notifiable disease lists, and given that most countries in the region share numerous risk factors for disease outbreaks, these highlighted diseases serve as a representative sample of priority diseases, conditions, and events for which national laboratory systems must develop diagnostic and confirmatory testing capabilities in Southeast Asia.

[1] As for sub-Saharan Africa, the list excludes syndromes based on case definitions without laboratory confirmation (e.g., diarrhea and tetanus).

Priority diseases in case study countries of Southeast Asia						
MBDS	**Cambodia**	**Lao PDR**	**Malaysia**	**Thailand**	**Timor-Leste**	**Vietnam**
chikungunya	acute jaundice	Chikungunya	Chancroid	Anthrax	acute watery	cholera
cholera	acute respiratory	cholera	cholera	cholera	diarrhea	dengue/DHF
dengue	infection	dengue	dengue	dengue	anthrax	H5N1influenza
diptheria	dengue fever	diptheria	diptheria	hemorrhagic fever	cholera	measles
encephalitis	diptheria	encephalitis	dysentery	diptheria	dengue	plague
H1N1/H5N1	measles	H1N1/H5N1	Ebola	dysentery	dysentery	SARS
influenza	meningoencephalitis	influenza	encephalitis	encephalitis	encephalitis/	typhoid/paratyphoid
leptospirosis	polio	leptospirosis	food-borne diseases	food-borne illness	meningitis	any outbreak
measles	rabies	measles	gonococcal	HFMD	measles	anthrax
meningitis	severe/acute	meningitis	infections	H5N1 influenza	polio	APC-adenovirus
PHEIC	diarrhea	polio	hepatitis	influenza	rabies	chicken pox zona
polio	bloody	PHEIC	HIV/AIDS	leptospirosis	tetanus	diarrhea
SARS	diarrhea	SARS	leprosy	measles	acute respiratory	diptheria
severe/acute	tetanus	severe/acute	malaria	meningococcal	diseases	amebic dysentery
diarrhea	unknown cluster	diarrhea	measles	meningitis	febrile illness	bacterial dysentery
tetanus		tetanus	mumps	pertussis	food-borne	dysentery syndrome
typhoid		typhoid	myocarditis	hospitalized	diseases	acute encephalitis
HIV/AIDS		HIV/AIDS	plague	pneumonia	hepatitis	viral hepatitis
malaria		malaria	polio	polio/AFP	HIV/AIDS	HIV/AIDS
pneumonia		pneumonia	rabies	rabies	influenza	leptospirosis
tuberculosis		tuberculosis	febrile illness	SARS	leprosy	malaria
			syphilis	neonatal tetanus	malaria	meningococcal
			tetanus	severe adverse events	pertussis	meningitis
			tuberculosis	following immunization	syphilis	mumps
			typhoid	acute severe illness/death	tuberculosis	pertussis
			typhus/rickettsioses	from unknown infection	typhoid	polio/AFP
			yellow fever	cluster of diseases		rabies
				with unknown		tetanus*
				etiology		
				viral hepatitis		
				HIV/AIDS		
				leprosy		
				malaria		
				tuberculosis*		
Plus 50 additional diseases not requiring immediate reporting						

National and regional priority diseases: Middle East/North Africa (MENA)

Although the WHO Regional Committee for the Eastern Mediterranean agreed to a regional framework for integrated disease surveillance and response more than 20 years ago, the Member States of the WHO Eastern Mediterranean Regional Office (WHO/EMRO) – which overlaps significantly with U.S. agency MENA designations – have not yet developed a regional implementation strategy.[32] In lieu of shared regional templates or protocols, WHO/EMRO has identified "visions" for controlling communicable diseases in the region, specifically targeting diseases that continue to take a toll in the countries that face resource constraints and ongoing challenges to stability and governance. This includes strengthening systems to prevent and detect endemic diseases that include tuberculosis, lymphatic filariasis, leprosy, dracunculiasis, malaria, schistosomiasis, leishmaniasis, ochocerciasis, trypanosomiasis, and maternal and neonatal tetanus, as well as vaccine-preventable diseases such as measles and polio.[33] Hepatitis and diarrheal disease caused by food- and water-borne illnesses continue to cause significant morbidity in these countries. In the last two decades, both developed and developing nations in the region have experienced zoonotic and emerging infectious disease outbreaks caused by viral hemorrhagic fevers, dengue fever, brucellosis, highly pathogenic H5N1 avian influenza, and the novel Middle Eastern Respiratory Syndrome (MERS) coronavirus.[34]

In response to these threats and to IHR reporting requirements, many countries in the MENA region have updated their national priority disease lists since 2005. Table 4 compares reportable diseases from three countries in the region: Egypt, Jordan, and Oman. Diseases are organized by immediacy of reporting requirements (immediately notifiable diseases, or those that must be reported within 24 hours, and those that must be reported either weekly or monthly). Diseases prioritized for reporting by all three countries, regardless of reporting immediacy, are highlighted.

Although this combined list does not necessarily represent a consensus for the entire region, it reflects shared priorities among countries with differing demographic and socioeconomic characteristics. Notifiable diseases that appear on all three lists served as a representative sample of priority diseases and conditions in the region for purposes of this report.

Priority diseases in case study countries of the Middle East/North Africa			
	Egypt[35]	**Jordan**[36]	**Oman**[37]
Immediate reporting	Acute Flaccid Paralysis/ Poliomyelitis	Acute Flaccid Paralysis (AFP) Poliomyelitis	Acute Flaccid Paralysis (AFP)
	HIV/AIDS	HIV/AIDS	
	Rabies	Rabies	Rabies
	Diphtheria	Diphtheria	
	Meningitis	Meningococcal disease	Meningococcal infection
	Plague	Plague	Plague
	Tetanus (Neonatal)	Neonatal tetanus	
	Acute Food Poisoning	Food poisoning	Food poisoning
	Unusually Severe Health Events: Botulism Viral hemorrhagic fever Rift Valley Fever Cholera Avian Influenza Other	Unexpected or unusual diseases or events Viral hemorrhagic fever Cholera	Severe Acute Respiratory Syndrome (SARS) Acute hemorrhagic fever syndrome Cholera
	Encephalitis		Haemophilus meningitis
		Suspected rubella & Congenital Rubella Syndrome	Congenital Rubella Syndrome
	Malaria		
		Suspected measles	Fever and rash-like illness
		Yellow fever	Yellow fever
		Pertussis	
Weekly or monthly reporting	Typhoid	Typhoid & paratyphoid	Typhoid & paratyphoid fever
	Brucellosis	Brucellosis	Brucellosis (human)
	Bloody diarrhea (dysentery)	Bloody diarrhea	
	Acute Hepatitis	Viral hepatitis	Acute viral hepatitis
	Animal bite	Animal bite	
	Fascioliasis	Chicken pox	Chicken pox
	Mumps		Mumps
	Pertussis		Pertussis
	Rubella		
	Schistosomiasis	Bilharziasis	Schistosomiasis
	Tuberculosis	Tuberculosis	Tuberculosis
	Filariasis	Cutaneous leishmaniasis	Leishmaniasis
	Leprosy	Diarrheas	Acute watery diarrhea (childhood)
	Measles	Hydatid cysts	
		Malaria	
		Sexually transmitted	HIV/AIDS

		diseases (STDs)	
		Tetanus	Active trachoma
		Viral meningitis	Meningitis (other than Hib and Nm)
		Adverse Events Following Immunization	Influenza and influenza-like illnesses (ILI)
		Bacterial (non-meningococcal) meningitis	LRTI and pneumonia

Appendix 2: Infection Control and Biosafety Guidelines

Author	Year	Title/Subject	Description
Infection Control and Prevention			
WHO	2014	Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care	IPC guidelines for acute respiratory infections, including those that might constitute a public health emergency of international concern
WHO Global IPC Network	2011	Tools for regional/national adaptation	1. IPC guidance for epidemic-prone infections 2. Implementation Tools 3. Generic IPC curricula for training of IPC professionals 4. Key IPC indicators for national and healthcare facility levels 5. Inventory of existing IPC national and international guidelines
WHO	2008	Interim Infection Control Recommendations for Care of Patients with Suspected or Confirmed Filovirus	IPC guidelines for Ebola and Marburg virus patients
WHO	2007	Standard Precautions in Patient Care	
WHO		Ethical Issues in Patient Safety	Antimicrobial resistance
US CDC	1996-present	Healthcare Infection Control Practices Advisory Committee	1. HICPAC Guidelines (1996) 2. Guideline for infection control in hospital personnel (1998) 3. Guidelines for environmental infection control in health-care facilities (2007) 4. Guideline for isolation precautions (2007) 5. Guideline for disinfection and sterilization in healthcare facilities (2008)

Laboratory biosafety			
WHO	2004	Laboratory Biosafety Manual – 3rd Edition	-Practical guidance on biosafety techniques for clinical laboratories -Available in multiple languages http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/
U.S. NIH and CDC	2009	Biosafety in Microbiological and Biomedical Laboratories (BMBL) – 5th Edition	Biosafety and biosecurity guidelines for research and diagnostic laboratories http://www.cdc.gov/biosafety/publications/bmbl5/
CDC	2012	Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories Recommendations of a CDC-convened, Biosafety Blue Ribbon Panel	Guidelines for diagnostic laboratories http://www.cdc.gov/mmwr/pdf/other/su6101.pdf
European Commission	2008	Biosafety Europe-Final Considerations: coordination, harmonization, and exchange of biosafety and biosecurity practices within a pan-European network	Guidelines and Regulations developed by the European Commission http://www.biosafety-europe.eu/FinalConsiderations_171208.pdf
Govt of Canada	2013	Canadian Biosafety Standards and Guidelnies	http://canadianbiosafetystandards.collaboration.gc.ca/cbsg-nldcb/assets/pdf/cbsg-nldcb-eng.pdf
CEN/ International	2011	CWA 15793	Process-based standard and implementation guidance for laboratory biological risk management http://www.internationalbiosafety.org/Organizations/fde5681c-ca94-4a20-

		827a-0716f524babc/Resources/Guidelines and Standards/Biorisk Management/Laboratory Biorisk Management CWA 15793.pdf
CEN/ International	CWA 153	Standards for professional biosafety training

Appendix 3: Natural Modes of Transmission

Disease	Pathogen	Potential Routes of Transmission				Vaccine
		Aerosol	Mucosal Membrane	Ingestion	Parenteral	
Anthrax	*Bacillus anthracis*	X	X	X	X	Yes
Brucellosis	*Brucella spp.*	X	X	X	X	No
Buruli ulcer	*Mycobacterium ulcerans*	U	X	X	X	No
Chikungunya	*Chikungunya virus*	X			X	No
Cholera	*Vibrio cholera*	X		X		No
Crimean Congo	*Crimean Congo Hemorrhagic Fever virus*	X	X		X	No
Dengue	*Dengue virus*	U	X		X	No
Diphtheria	*Corynebacterium diphtheria*	X	X	X	X	Yes
Ebola virus disease	Ebola virus	U	X		X	No
Hepatitis A & E	Hepatitis A & E virus			X	X	Yes/No
Hepatitis B, C, & D	Hepatitis B, C, & D virus		X		X	Yes/No/Ind.
HIV	HIV		X		X	No
Influenza	Influenza virus	X	X			Yes
Japanese Encephalitis	Japanese encephalitis virus	X	X		X	Yes
Lassa Fever	Lassa fever virus	X	X	X	X	No
Leprosy	*Mycobacterium leprae*	U	X	X	X	No
Lymphatic filariasis	*Wuchereria bancrofti / Brugia malayi*			X	X	No
Malaria	*Plasmodium falciparum*				X	No
Marburg fever	Marburg Virus	U	X		X	No
Measles	Measles virus	X	X		X	Yes
Meningococcal meningitis	*Neisseria meningitidis*	X	X	X	X	Yes
MERS	MERS Co-V	X	X		X	No
Onchocerciasis	*Onchocerca volvulus*				X	No
Plague	*Yersinia pestis*	X	X	X	X	No
Polio	Poliovirus	X		X	X	Yes
Rabies	Rabies virus	X	X		X	Yes
Rift Valley fever	Rift Valley fever virus	X	X		X	Not for humans
SARS	SARS Co-V	X	X			No
Shigella	*Shigella dysenteriae*	U	X	X	X	No
Trypanosomiasis	*Trypanosoma spp.*				X	No
Tuberculosis	*Mycobacterium tuberculosis*	X	X	X	X	Yes, limit efficacy
Typhoid	*Salmonella typhi*	U	X	X	X	Yes
West Nile Fever	West Nile Fever virus	X	X		X	No
Yellow Fever	Yellow fever virus	X	X		X	Yes

Appendix 4: Development of an Epidemiologic Model for Community Risk Posed by Development of Clinical Laboratory Capability

The calculations in the main body of this report (above) represent a semi-quantitative scale for depicting risk based on existing biosafety frameworks and references. However, as part of this study, we tested the proof of concept that biological risk could be estimated quantitatively to give a numerical score, with the goal of allowing decision-makers to perceive relative risk rapidly.

To develop a quantitative model for laboratory biological risk that assesses the overall community risk or health security risk incurred by specific manipulations on specific pathogen samples, we employed a classical risk assessment relationship:

$$R=f(T, V, A) \qquad \text{(Eq. 4.1)}$$

Wherein risk (R) is a probability that a threat (T) will exploit a vulnerability (V) to cause harm to an asset (A). Calculation of T, V, and A will enable us to assess the risk of a pathogen to cause serious infection as the result of an occupational manipulation, and the potential danger of the pathogen to the community at large.

> Threat (*T*) of a pathogen: the likelihood that a pathogen will be transmitted to a worker during a given manipulation or procedure.
>
> Vulnerability (*V*) of the subject: the impact of the pathogen or disease on an exposed subject
>
> Asset (*A*): the degree to which the pathogen impacts the community at large

T, V, and A are approximated by epidemiologic parameters, as described below, and Risk is calculated as the product of all variables.

$$Risk = T \times V \times A \qquad \text{(Eq. 4.2)}$$

In this model, *V* is measured by the severity of disease caused by a pathogen. To approximate *V*, we employed the average case fatality rate (CFR), which is defined as the proportion of people with a specific condition who die as a result of that condition (or the number of deaths from a specific disease over the number of cases of disease within a given time frame).[38] Because values for CFR are a proportion or ratio, they can range from 0 to 1, with 1 indicating disease that is certain to result in death. For our analysis, *V* values are therefore constant for a specific pathogen and independent of how the sample is handled or manipulated. For pathogens that do not generally cause mortality, we estimate *V* as *0.01*. *V* represents an average vulnerability and does not make assumptions about risk factors such as patient immune status, which would impact the vulnerability of a patient. Moreover, *V* assumes that

no medical countermeasures or vaccines are applied.[2] We display *V* values for priority pathogens in Table 4.1.

A represents the average number of cases likely to result if an individual becomes infected with a communicable disease and transmits that disease to others. We approximate this value using the basic reproductive rate (R_0), or the expected number of secondary cases of an infectious disease resulting from an index case in a completely susceptible population.[39] Using R_0 enables us to quantitate the potential for a pathogen to cause an outbreak and measures the magnitude of a potential health security threat to the community at large. Because the index case, or original individual infected is also considered an asset in our model, $A = R_0 + 1$. In cases where pathogens are not transmitted naturally from person to person, but require an intermediate host, such as a mosquito, we estimated $R_0 = 1$, a value that assumes an intermediate host density.[40] Of note, for water-borne diseases, in countries with treated water supplies, R_0 would likely be lower than published values, leading to lower A values than in Table 4.1.

As with *V*, *A* is pathogen-specific variable and constant throughout our analysis. Both variables are listed in Table 4.1. Mitigation of epidemic potential of any pathogen can be reduced by provision of vaccines to the population at large,[41] or by post-exposure administration of medical countermeasures such as anti-microbial drugs. When available, medical countermeasures can provide significant post-exposure protection and significantly reduce *A* values.

While *A* and *V* are epidemiologic parameters that remain constant for each pathogen, *T* is a function of the hazard posed by sample manipulation processes (*M*) (for example, sample collection or diagnostic testing activities) and the ability of a pathogen within a given sample to cause infection (*I*). In a laboratory setting, workers may be exposed to pathogens through routes other than the normal routes of pathogen infectivity: aerosol, mucous membrane or cutaneous exposure (mucocutaneous), insect bite, or ingestion. In addition, laboratory workers may be exposed to larger amounts of pathogen than general encountered during transmission of illness in a community setting. For example, inhalation of large quantities of a virus usually transmitted by insect vectors can result in infection via mucocutaneous or aerosol routes.[42] Therefore, the value for *T* accounts for the likelihood that exposure will result from a given manipulation during one of several stages of laboratory assessment, and the likelihood that an exposure will result in infection of laboratory personnel.

In this model, T is approximated as a product of the manipulation hazard (*M*) and the likelihood that an exposure will cause infection (*I*).

$$T = M \times I \qquad \text{(Eq. 4.3)}$$

[2] Administration of vaccines or medical countermeasures to laboratory workers significant reduces vulnerability and thereby decreases overall risk.

As diagrammed in Figure 2, various stages of a laboratory system necessitate different occupational manipulations by workers that will introduce different likelihoods of exposure to dangerous pathogens. Manipulations can lead to exposure via percutaneous, mucocutaneous, and aerosol routes. The manipulation hazard associated with a specific procedure, $M_{procedure}$, depends upon the specific manipulation of a pathogenic sample and is unique for different laboratory-related processes. Notably, intentional exposure has occurred in clinical laboratories but because the incidents are quite rare, it represents a negligible manipulation hazard for laboratory biological risk. Using prospective data, several investigators have assessed relative rates of injury associated with specific occupations. Based on these rates, we developed procedure-specific manipulation values for sample collection and laboratory diagnostic procedures of clinical laboratory systems.

The ability of a pathogen to cause infection depends on multiple factors, including the infectious dose of a pathogen, the concentration of the pathogen within the sample, and the physical parameters of the sample that impact transmission. Because of the paucity and ethical constraints in determining data on infectious dose in human populations, in addition to wide ranges for presumed pathogen concentrations, and unpredictable differences in physical specimen parameters, it is impossible to empirically calculate *I* accurately for all pathogens. *I* can be approximated by epidemiologic constants for exposure-associated attack rates for specific pathogens and different working conditions. However, because attack rates are influenced by several factors including prevalence of disease, workload, specific occupation, etc., rates would ideally be calculated in member countries. For our analysis, we have conducted a literature review for exposure associated attack rates (*E*) for infectious diseases among laboratory workers. Because data is compiled prospectively and exposed worker data (denominator) is not consistent across studies, the values are only estimates used to illustrate the model. Data from historical studies[43],[44] is normalized and displayed in Table 4.1. In cases where no data for *E* is available, we estimate *E* based on attack rates for similar pathogens; estimated values are denoted by italics in the table. *E* values are specific for each pathogen and remain constant throughout our analysis.

Therefore in our analysis, *I* is approximated by *E*, and equation 6 becomes:

$$T = M_{procedure} \times E_{pathogen} \qquad \text{(Eq. 4.4)}$$

To estimate the overall risk posed by accidental release of a pathogen during routine laboratory processes, our R score is defined as the product of:

$$Risk = M_{procedure}\ (exposure) \times E\ (exposure\text{-}associated\ attack\ rate) \times V\ (case\ fatality) \times A\ (R_0 + 1)$$

(Eq. 4.5)

In our analysis, Risk is measured in units of deaths –year. The numerical values for risk enable one to perform a comparative assessment of occupational laboratory risks to health security within a given system.

Table 4.1: Pathogen-specific values for V, A, I – examples

Pathogen	Disease	V	A	I
Bacillus anthracis	Anthrax	0.2	1	0.012
Brucella spp.	Brucellosis	0.02	1	0.18
Mycobacterium ulcerans	Buruli ulcer	0.01	1	0.05
Vibrio cholera	Cholera	0.01	3.6	0.05
Chikungunya virus	Chikungunya fever	0.01	2	0.05
Crimean Congo virus	Crimean Congo hemorrhagic fever	0.3	2	0.6
Dengue virus	Dengue (hemorrhagic) fever	0.01	1	0.05
Corynebacterium	Diptheria	0.07	7.5	0.6
Ebola virus	Ebola virus disease	0.85	1	0.65
Human Immunodeficiency virus	HIV/AIDS	0.85	2	0.03
Influenza virus	Influenza	0.5	3.5	0.45
Lassa Fever virus	Lassa Fever	0.5	1	0.65
Mycobacterium leprae	Leprosy	0.01	1	0.06
Wuchereria bancrofti / Brugia malayi	Lymphatic filariasis	0.01	1	0.05
Plasmodium falciparum	Malaria	0.2	1	0.05
Yersinia pestis	Plague	0.6	3	0.45
Marburg virus	Marburg hemorrhagic fever	0.8	2.6	0.65
Measles virus	Measles	0.1	15	0.65
Neisseria meningitidis	Meningitis	0.11	2.3	0.11
Poliovirus	Polio	0.1	1	0.05
Yersinia pestis	Plague	0.7	2.3	0.45
Rabies virus	Rabies	0.99	1	0.5
SARS coronavirus	SARS	0.4	4.5	0.65
Shigella dysenteriae	Shigella	0.08	2.3	0.65
Trypanosoma spp.	Trypanosomiasis	*1*	*1*	*0.05*
Salmonella Typhi	Typhoid	0.1	3.5	0.05

Mycobacterium tuberculosis	Tuberculosis	0.3	7	0.6
West Nile virus	West Nile fever	0.33	2	0.05
Japanese Encephalitis virus	Japanese Encephalitis	0.6	2	0.05
Yellow Fever virus	Yellow Fever	0.2	2	0.05
Rift Valley Fever virus	Rift Valley Fever	0.7	1	0.65

Calculating risk for sample collection

To apply this model, we calculated overall risks for sample collection and diagnostic testing of priority pathogens. With values for *I*, *A*, and *V* as constants, this required calculation of procedure-specific manipulation hazards. For whole blood, CSF, pleural fluid, and bone marrow, the specimen is collected via syringe directly into a sealed tube, posing a risk of parenteral inoculation. Swab specimens can be taken from a skin lesion or wound exudate, nose, throat, nasopharynx, trachea, and tissue. The primary risk involved with this method of collection includes exposure to the laboratory worker's epithelium (mucous membranes and/or intact or non-intact skin). Biopsies and some skin samples require a skin punch and pose a potential risk of parenteral exposure due to injection of local anesthesia, use of a scalpel or blade to incise the skin sample, and suture needle to close larger biopsy sites. Due to risks of contact with skin and spray into eyes, biopsy also poses a risk for mucocutaneous exposure. Collection cups are used for urine, stool, and sputum samples and pose a primary risk of mucocutaneous exposure. Furthermore, workers tasked with assisting in collecting sputum samples have been shown to have higher rates of exposure, presumable due to aerosol exposure. Phlebotomists, technologists, and nurses responsible for sample collection are also exposed to patients and are therefore likely to acquire disease via human-human transmission. While this risk is significant, for the purposes of this assessment, we do not include the risk of person-person transmission in our analysis for sample collection. Manipulation values (*M*) enable quantitation of specific occupational hazards associated with laboratory duties. Importantly, *M* values can be significantly reduced upon application of standard and transmission based procedures that minimize the likelihood of exposure to dangerous pathogens.

To approximate values for $M_{\text{sample collection}}$, we calculated manipulation hazards posed by sample collection procedures (Tables 4.2 a-c). We reviewed data on prospective studies analyzing blood and body fluid exposure in workers responsible for clinical sample collection to determine relative risks posed by common manipulations. Risks posed by sample collection include risk of exposure via parenteral, mucocutaneous, and aerosol routes. Parenteral transmission (i.e., sharps injuries such as needle sticks and accidents that occur while biopsying samples) pose the largest risk for accidental infection. Mucocutaneous exposure, or exposure via vulnerable epithelial surfaces such as mucous membranes or skin, represents another significant route of entry. In cases where samples are collected in a non-sealed vessel or workers are exposed to droplets from patients due to the sample collection procedure, aerosolization also represents a risk. Although several studies have been conducted to assess health care worker exposure to blood and body fluids, we used exposure risks derived from study of healthcare workers in the Duke University healthcare system.[45] This study analyzed a large population and

stratified risks for exposure to blood and body fluids by work function (e.g. sample collection and diagnostics). Based on this data, we were able to surmise values for percutaneous and mucocutaneous exposure. Although specific data on aerosol exposure was not determined presumably due to difficulties in identifying aerosol exposure post-facto, we estimated exposure risks for percutaneous, mucocutaneous and aerosol exposure for laboratory workers. Probabilities for exposure via each route are provided below, with overall manipulation hazards determined by adding probabilities of infection via different routes. Of note, although we have been able to estimate manipulation hazards, a comprehensive prospective study on injury rates for those collecting patient samples would provide more accurate information. As shown, the highest threat was posed by pathogens collected by biopsy as that entails use of sharps as well as potential aerosol and mucocutaneous exposure, with phlebotomy also causing high risk due to the inherent danger of self-injection.

Table 4.2a

Mucus Membrane (M)	0.4
Aerosol (A)	0.4
Parenteral (P)	0.92

Table 4.2b

Syringe	P	0.92
Collection Cup	A, M	0.8
Biopsy	P, A, M	1.0
Swab	A, M	0.8

Table 4.2c

	P	**M**	**A**	**Total Manipulation Hazard/FTE/Year**	**Total Manipulation Risk (FTE/YEAR)**
Syringe	X			.091	0.96
Swab		X	x	.008	0.8
Collection cup		X	x	.008	0.8
Biopsy	X	x	x	.099	1
Rate/FTE/Year	.091	0.004	0.004		
	.096	.003	.003		

Abbreviations: FTE (full time employee equivalent); P (percutaneous); M (mucocutaneous); A (asset)

Having estimated the values for each of our parameters, we used Equation 8 to calculate the laboratory biological risk score for each specimen of each pathogen and averaged the specimen scores for each pathogen.

These scores do not reflect the use of vaccines or medical countermeasures that would reduce the risk scores for many pathogens. Additionally, they do not assume strict adherence to standard and

transmission-based precautions, which are critical factors in reducing biological risk. Laboratory-acquired infections have been attributed to needle sticks, other sharps injuries, not wearing gloves, not sanitizing the outside of specimen or culture containers, etc. Several studies have assessed the impact of standard protocols, training, and protective equipment on the incidence of laboratory acquired infections in healthcare workers and have demonstrated that standard and transmission-based precautions reduce rates of acquired infections by 20-60%.[46]

Calculating Risk for Clinical Laboratory Analysis

Clinical laboratory testing requires manipulation of samples and exposure and use of equipment that is different from that used for sample collection. Based on the results of Dement et al.,[47] we calculated manipulation risks for procedures conducted routinely by laboratory technicians for the priority diseases identified in the notional priority disease list described in the main body of this report. Aerosol exposure was not measured in the Duke study. Based on historical data, we estimate that aerosol exposure likely accounts for the vast majority of unexplained exposures and can account for approximately 50% of the overall exposure hazard for those collecting samples. During laboratory testing, pathogens can be transmitted via aerosol as a result of processes including pipetting, centrifugation, and culture manipulation; we estimate that approximately 40% of exposure is due to aerosol exposure, with 2% attributable to centrifugation accidents.[48] Manipulation hazards for different experimental procedures were calculated by adding the manipulation hazards for percutaneous, mucocutaneous, or aerosol exposure. The data is summarized in Table 4.3. Using this data, we developed an approximation for $Threat_{Diagnosis}$ that represents the hazard incurred by each diagnostic procedure.

Table 4.3 – Risk based on collection method and manipulation hazard according to diagnostic testing algorithms – examples					
Pathogen	**Sample**	**Collection**	**VAI**	**Manipulation Hazard**	**Risk**
Bacillus anthracis	Blood	Syringe	0.0024	0.92	0.002208
	Skin lesion exudate	Swab	0.0024	0.8	0.00192
	CSF	Syringe	0.0024	0.92	0.002208
	Pleural fluid	Syringe	0.0024	1	0.0024
	Sputum	Collection cup	0.0024	0.8	0.00192
	Urine/feces	Collection cup	0.0024	0.8	0.00192
Brucella spp.	Blood	Syringe	0.0036	0.92	0.003312
	Bone marrow	Syringe	0.0036	0.92	0.003312
	CSF	Syringe	0.0036	0.92	0.003312
	Wound fluid/pus	Swab	0.0036	0.8	0.00288
Mycobacterium ulcerans	Blood	Syringe	0.0005	0.92	0.00046
	Bone marrow	Syringe	0.0005	0.92	0.00046
	CSF	Syringe	0.0005	0.92	0.00046
	Wound fluid/pus	Swab	0.0005	0.8	0.0004
	Biopsy	skin punch	0.0005	1	0.0005
Chikungunya virus	Serum	Syringe	0.001	0.92	0.00092
Vibrio cholera	Stool	Culture	0.0018	0.8	0.00144
Crimean Congo Hemorrhagic Fever virus	Blood, serum	Syringe	0.036	0.92	0.03312
	Tissue/skin	skin punch	0.036	1	0.036

	biopsy				
Dengue virus	Blood, serum	Syringe	0.001	0.92	0.00092
Corynebacterium diphtheriae	Nose, throat, or wound swabs	Swab	0.315	0.8	0.252
Ebola virus	Whole blood, serum,	Syringe	0.5525	0.92	0.5083
EV71	Stool,	Collection cup	0.03	0.8	0.024
	Throat swab	Swab	0.03	0.8	0.024
Hepatitis A	Blood	Syringe	0.0015	0.92	0.00138
Hepatitis B	Blood, serum	Syringe	0.006	0.92	0.00552
Hepatitis C	Blood, serum	Syringe	0.001	0.92	0.00092
HIV	Blood, serum	Syringe	0.051	0.92	0.04692
Influenza virus	Throat, nasal, nasopharyngeal, trachea	Swab	0.7875	0.8	0.63
	Nasopharyngeal aspirate	Mucus trap	0.7875	0.8	0.63
	Broncholavage fluid	Bronchoscope and saline	0.7875	0.8	0.63
	Blood	Syringe	0.7875	0.92	0.7245
Lassa Fever Virus	Blood, serum	Syringe	0.325	0.92	0.299
	Tissue	skin punch	0.325	1	0.325
Mycobacterium leprae	Skin smear	Swab	0.0006	0.8	0.00048
Wuchereria bancrofti / Brugia malayi	Whole blood	Syringe	0.0005	0.92	0.00046
Plasmodium falciparum	Whole blood	Syringe	0.02	0.92	0.0184

Marburg virus	Whole blood, serum	Syringe	1.352	0.92	1.24384
	Tissue	Swab, skin punch	1.352	1	1.352
Measles virus	Urine	Collection	0.975	0.8	0.78
	Nasopharyngeal aspirate	Mucus trap	0.975	0.8	0.78
	Blood	Syringe	0.975	0.92	0.897
	Throat swab	Swab	0.975	0.8	0.78
Neisseria meningitidis	CSF	Syringe	0.1265	0.92	0.11638
	Blood	Syringe	0.1265	0.8	0.1012
Yersinia pestis	Whole Blood	Syringe	0.7245	0.92	0.66654
Poliovirus	Stool	Collection cup	0.035	0.8	0.028
	Pharynx swab	Swab	0.035	0.8	0.028
Rabies virus	Brain (post-mortum)	Biopsy	0.495	1	0.495
Rift Valley fever virus	Blood	Syringe	0.455	0.92	0.4186
SARS coronavirus	Stool,	Collection cup	1.17	0.8	0.936
	nasopharyngeal swab	Swab	1.17	0.8	0.936
Shigella dysenteriae	Stool	Collection cup	0.0092	0.8	0.00736
Trypanosoma spp.	Whole blood	Syringe	0.0495	0.92	0.04554
	lymph node aspirates	Syringe	0.0495	0.92	0.04554
	CFS	Syringe	0.0495	0.92	0.04554
Mycobacterium tuberculosis	Sputum	Collection cup	1.26	0.8	1.008

Salmonella typhi	Stool sample	Collection cup	0.0175	0.8	0.014
	Blood	Syringe	0.0175	0.92	0.0161
	Bone marrow	Syringe	0.0175	0.92	0.0161
	Urine	Collection cup	0.0175	0.8	0.014
West Nile virus	Whole blood, serum, plasma, tissue	Syringe	0.033	0.92	0.03036
Yellow Fever virus	Whole blood, serum, plasma, tissue	Syringe	0.033	0.92	0.03036
Japanese Encephalitis virus	Whole blood, serum, plasma, tissue	Syringe	0.033	0.92	0.03036

Finally, using the framework for appropriate screening, diagnostic, and confirmatory tests to be conducted at each level of a tiered, integrated laboratory system (see description in main body of this report), we identified the tests most likely to be conducted at health service levels 1 (local health facility), 2/3 (intermediate, such as district/provincial), and 4 (central reference laboratory) for the pathogens listed in the notional priority disease list to develop an aggregate risk score for the testing platforms likely to be established at each level of the laboratory network, summarized in Table 4.4.

Table 4.4: Risk scores by diagnostic test and service level				
Service Level	**Diagnostic Test**	**Risk Scores**		Likely exposure risk
		Average	Range	
1	Rapid Test	0.01152	.0005-.078	**P/M**
1-2	Microscopy	0.09452	.0002-.504	**P/M**
2-3	Agglutination (serology)	0.08364	.0014-.315	**P/M**
2-3	ELISA (serology)	0.15363	.00021-.568	**P/M**
2-3	Bacterial Culture/Isolation/Serotype	0.28606	.0004-1.08	**P/M/A**
2-3	PCR/RT-PCR	0.04469	.0006-.162	**P/M**
2-3	Virus neutralization	0.18693	.00021-.568	**P/M/A**
3-4	Antimicrobial susceptibility	0.24693	.013-.567	**P/M/A**
3-4	Immunofluorescence	0.28681	.208-.331	**P/M**
4	Immunohistochemistry	0.26063	.00031-.838	**P/M**

P = parenteral; M = mucosal; A = aerosol

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